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TRANSACTIONS & STUDIES

*of the*

College of Physicians of Philadelphia

Volume 13
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# Penicillin—Its Present Status in the Treatment of Infections[1,2]

*By* CHESTER S. KEEFER, M.D.

*Professor of Medicine, Boston University, and Director, Evans Memorial Hospital, Boston*

SEVERAL weeks ago, a young woman was admitted to our Clinic at the Evans Memorial complaining of chills and fever. She had been well until three days before admission when there was a sudden departure of health. Upon examination, it was found that she had high fever, pain in the right ankle joint, and the physical signs of a bilateral bronchopneumonia. The blood culture showed numerous colonies of *Staphylococcus aureus*. She was placed on penicillin therapy at once. Within the first two days the temperature was reduced to a lower level, but she developed a right sided hemiparesis with aphasia, and the signs of an acute arthritis of the right ankle joint. Gradually over a period of three weeks the temperature returned to normal, the other signs of infection disappeared and she made a complete recovery with the exception of a slight weakness of the right arm. The course of this patient's illness illustrates what can be accomplished in 90% of all cases of *Staphylococcus aureus* infections with bacteremias when penicillin is given in adequate amounts for a sufficiently long period of time. When one recalls that the fatality rate in this disorder is usually between 50% and 75% without penicillin, it is plain that penicillin has completely changed the outlook in this group of infections. But this is not all. It can be said without reservation that penicillin is the most remarkable chemotherapeutic agent that has been discovered up to the present time. When one makes such a statement it is well to document it. In the first place, it is a substance of extremely great antibacterial power. One milligram of crystalline penicillin is capable of inhibiting the growth of staphylococci in 82.5 liters of broth. It is non-toxic in maximum therapeutic doses in man. It is highly effective against a wide variety of microorganisms of the gram-positive group. It is effective in both gonorrhea and syphilis, the two commonest genito-infectious diseases. It is responsible for the reduction of the fatality rate in more diseases than any other chemotherapeutic agent; it shortens the clinical course of many infectious disorders, and it saves many days of illness and disability. When one realizes that this can be accomplished by an agent that destroys bacteria and other micro-organisms such as the

[1] Nathan Lewis Hatfield Lecture XXIX, The College of Physicians of Philadelphia. Delivered before a joint meeting of the College and the Philadelphia County Medical Society, February 7, 1945. Printed in the Society's publication, *Philadelphia Medicine*, March 24, 1945.

[2] From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

*Treponema pallidum* without injuring the tissues of the host, it deserves to be called remarkable. No other known agent can do as much.

There are many fascinating historical events to be recorded in the development of penicillin. At this time three years ago, there was not enough penicillin in this country to treat a single patient. Two years ago, only 100 patients had received treatment. Today there is enough penicillin being produced in this country alone to supply our Armed Services and those of our Allies, and a moderate amount for civilians. This progress has been due to the combined efforts of many groups working in universities, hospitals, in industry and in government.

Tonight I want to review for you the present status of penicillin treatment in the common infections. First of all, I shall make a few remarks concerning the best route of administration. There are two salts of penicillin available for clinical use, the sodium and the calcium salts. They are both equally effective therapeutically and they can both be used interchangeably. The commonest route of administration is the intramuscular, and it is the route of choice. Injections may be given intermittently or continuously. It may also be given intravenously, and topically into the serous cavities, joint cavities, or into the subarachnoid space.

In an attempt to delay absorption from local deposits in the muscles, penicillin has been combined with beeswax and peanut oil or with gelatin and vasoconstrictor drugs. These methods show considerable promise and when the details have been worked out, the use of such a method will undoubtedly reduce the number of injections required to maintain adequate concentrations of penicillin in the blood and tissues.

When penicillin is given by mouth, the coefficient of absorption is small and varies between 2 and 10%. When large amounts are given by this route and at frequent intervals in oil, or in buffers such as sodium citrate, a sufficient amount is absorbed to influence the course of infections. In the case of gonorrhea or lobar pneumonia, recovery may be observed following the use of 5 to 10 times as much as is needed when penicillin is given parenterally. At present the use of penicillin by mouth is wasteful, uncertain and expensive, when compared to other routes of administration.

*Dosage.* It is difficult, and indeed impossible, to make any absolute rules concerning the necessary dosage of penicillin that will be universally applicable. The daily and total dose will depend upon the type of infection, its location, the presence of bacteremia, the age and the clinical condition of the patient and the course of the disease.

For example, it is a well established fact that there is a wide variation in the susceptibility of various organisms to penicillin. The gonococcus is the most sensitive organism so that between 50,000 and 150,000 units will cure 98 per cent of cases of gonorrhea within 24 hours. The hemolytic *Staphylococcus aureus* is more resistant, so that between 100,000 and 200,000 units a day for one to three weeks or longer may be required. In the case of bacterial endocarditis due to *Streptococcus viridans*, at least 300,000 units daily for a period of 14 to 21 days may be considered a minimum dose.

One of the greatest difficulties in assessing dosage is the lack of signs of toxicity so that the maximum tolerated dose is not known. Conversely the minimum effect dose is difficult to define in all cases. The most reliable guides to dosage are the type of specific organism and the response of the patient to treatment.

### Generalized Infections with Bacteremia

Generalized infections with bacteremia due to susceptible organisms, such as the *Staphylococcus aureus*, *Streptococcus hemolyticus* or the *Pneumococcus*, respond in a most favorable manner to penicillin. The outlook in individual cases will depend to some extent upon such factors as the source of the primary infection, the age of the patient, the period at which treatment is begun and, in some instances, the accessibility of the infection to surgical treatment. The best results have been obtained in young individuals who have a recent infection and who have been given active and intensive treatment with 120,000 to 240,000 units a day. Less favorable results have been seen in elderly patients with overwhelming infections, bacterial endocarditis, meningitis, or when the infection is associated with some complicating debilitating disease.

In the case of staphylococcic bacteremia, the overall fatality rate has been reduced to within 10 to 20 per cent. It has been lowest in young persons with osteomyelitis (10 per cent) and highest in those with bacterial endocarditis (75 per cent).

In all cases with bacteremia the treatment should be continuous for two to three weeks and enough

penicillin should be given daily to bring the infection under control.

### Infections of the Meninges

*Meningococcus Meningitis.* Sulfadiazine continues to be the drug of choice in the treatment of meningococcic meningitis. While penicillin is effective in controlling this disease, the response is slower than following the sulfonamides, and it continues to be necessary to give penicillin both systemically and intrathecally. In cases failing to respond to the sulfonamides within a period of 24 to 48 hours with adequate treatment, penicillin should be started at once. Penicillin is the drug of choice in the treatment of all infections of the meninges due to the pneumococcus, staphylococcus, and the hemolytic streptococcus. Treatment should be started as soon as the diagnosis is established, and all foci of infection in the neighborhood which can be drained surgically should be attacked at the same time. This is especially true when there is an associated mastoiditis or lateral sinus thrombosis.

*Pneumococcus Meningitis.* Pneumococcus meningitis is always a serious disease. Before the days of the sulfonamides it was invariably fatal. Now a certain number of patients—that is, between 40 and 50 per cent—recover following the use of either the sulfonamides or penicillin. There is some evidence that the combination of sulfadiazine and penicillin may be better than either drug alone (1).

One of the reasons that pneumococcus meningitis is such a serious disease is that it is frequently a metastatic lesion following pneumococcus lobar pneumonia with or without an associated bacterial endocarditis. In other cases it follows craniocerebral injuries, otitis media and/or mastoiditis or suppurative sinusitis of the ethmoid or sphenoid cells. Another reason for the severity of this infection is that it tends to produce hydrocephalus and an encephalitis which may lead to cerebral atrophy and profound neuropsychiatric disturbances.

### Otitis Media and Mastoiditis

Patients with otitis media and mastoiditis respond to penicillin treatment most favorably. In the case of mastoiditis, simple mastoidectomy followed by closure of the incision with the insertion of a small catheter so that penicillin can be instilled into the cavity for three or four days is the method of choice, as demonstrated by Johnson, Weinstein and Spence (2). Under these conditions healing takes place rapidly and the postoperative course is greatly shortened.

### Tonsillitis

Tonsillitis resulting from hemolytic streptococcal infection responds very promptly to the use of penicillin. Treatment should be continued for at least 5 to 7 days in order to prevent relapses. One of the striking features following the treatment is the rapid decrease in the number of organisms in the throat. Indeed, it is often difficult to recover streptococci from the local focus of infection 24 or 48 hours after treatment is started. If, however, there is an interruption of treatment, there may be relapses of infection and organisms will reappear in great numbers in the throat. For this reason, it is essential that the treatment be continued for at least several days after all signs of acute infection have subsided.

### Pneumococcus Pneumonia

The pneumococcus is extremely susceptible to the action of penicillin *in vitro* and when patients with pneumococcus lobar pneumonia receive penicillin, the outcome is extremely favorable. Tillett, Cambier and McCormack (3) have recorded a fatality rate of only 6.5 per cent in 106 cases, and in all of the fatal cases there were complicating factors. Meads, Harris and Finland (4) record favorable results in cases in which the sulfonamides had previously failed to control the infection. The latter group of investigators found that penicillin was equally effective in the patients who had received it alone or in those who had failed to respond to the sulfonamides.

There are a number of points worth commenting on with respect to the treatment of pneumococcus lobar pneumonia with penicillin. When patients are treated early in the course of their disease—that is, within the first 24 or 48 hours, there is usually a decrease in the temperature and pulse rate within the first 24 to 48 hours and preceding these objective signs, the patients feel improved subjectively.

Bacteremia, if present, disappears promptly, usually following the first injection, and purulent complications following the use of penicillin are exceedingly uncommon. They were not observed by Meads, Harris and Finland in any of their cases.

The dosage and duration of treatment will vary from one patient to another, depending upon the

clinical response and the severity of the infection. In some mild cases, a satisfactory response has been observed following 60,000 to 80,000 units a day for two days, given in doses of 10,000 units every 3 or 4 hours. In other cases, the equivalent of at least 15,000 units every 2 hours for the first 12 or 24 hours, after which longer intervals or smaller amounts may be used for another 2 or 3 days. It is wise and sound practice to continue treatment for 2 or 3 days after the temperature has reached normal in order to avoid relapses which may be observed if treatment is stopped abruptly after the first 48 or 72 hours. Certainly the total dosage during the first 24 hours must be gauged by the condition of the patient and his response to the treatment.

In attempting to assess the conditions in which the sulfonamides or penicillin should be used in the treatment of pneumococcus lobar pneumonia, it is not possible at the time of this writing to make any definitive rules. Both agents are effective. However, the sulfonamides can be given by mouth and penicillin must be given parenterally. This may be a consideration in some cases. However, it is well to recall that penicillin is non-toxic and that the sulfonamides may cause side reactions. In general, it can be said that penicillin is the drug of choice in (1) all patients who have failed to respond to the sulfonamides after 24 hours of treatment, (2) all patients with a persistent bacteremia, (3) all patients who show a spread of the process, (4) all patients who develop any signs of sulfonamide intoxication or renal irritation, and (5) all patients who have leukopenia or who develop auricular fibrillation, delirium tremens or other complications during the infection.

It is well to start with penicillin when the patient is acutely ill or has developed a shock-like state, or when he has some complicating disease such as renal, hepatic, or cardiac disorder, or when there is leukopenia or a history of sensitivity to the sulfonamides.

In brief, it can be said that penicillin can be given with greater safety than sulfadiazine and with the same good results. It will gradually become the drug of choice in the treatment of all cases of pneumonia.

### Subacute Bacterial Endocarditis

When subacute bacterial endocarditis due to the nonhemolytic streptococcus was first studied, the results of treatment on the clinical course were discouraging. In some cases, when 30,000 to 60,000 units were given daily, the blood was cleared of organisms and the temperature was reduced for the period of treatment. However, the course of the disease was not otherwise influenced and when the drug was withdrawn, the bacteremia recurred and progressive signs of infection ensued. It is now known that these results were due to an inadequate amount of penicillin. When larger amounts of penicillin are given for longer periods of time—that is, 200,000 or 300,000 units a day for at least 3 weeks—there will be a clinical arrest of the disease varying from 1 to 10 months in about 55 per cent of cases. (See Figure 1.) A certain number of patients will die before adequate treatment as described above has been completed. Death in these cases is due to the infection, to embolism or to acute heart failure.

When clinical arrest takes place, the following sequence of events may be observed. Within 24 to 72 hours after treatment is started, the patients often lose many of the constitutional symptoms of infection. The anorexia disappears, the appetite improves, and the patient becomes more interested in his surroundings. The temperature is promptly reduced in some cases to within normal limits within the first week. In others, after the initial decrease in temperature, the fever may continue for a 6 to 8 week period as low grade fever. In a third group, it may go down only after 2 to 3 weeks. Prolonged fever after beginning treatment may be due to an infection by a relatively resistant organism, or it may be due to a complication or a continuing tissue reaction. Once the temperature becomes normal, there may be occasional recurrences due to embolic phenomena.

Within 1 to 5 days after treatment, the blood cultures generally become negative and remain so except for occasional instances when a transitory bacteremia and embolic phenomena occur.

Petechial hemorrhages may continue to occur for 6 to 8 weeks after treatment is started and emboli may occur up to 2 months. The spleen decreases in size, the leukocytes decrease in number, anemia improves, clubbing of the fingers may recede.

As might be anticipated, there are no changes in the signs of valvular disease and the renal lesions are not favorably influenced by treatment. It is now well established that all of these favorable results may be obtained with penicillin alone and no anti-coagulant such as heparin is necessary.

Following a clinical arrest, the patient may return to apparently normal health in that the symptoms and signs of infection are absent. Some patients have recurrences as long as six to nine months after treatment. Many patients die of cardiac insufficiency without signs of active infection.

conditions, the lesions in the bone frequently recalcify and complete healing takes place without incision and drainage.

When the infection has spread into a neighboring joint, it is desirable to perform whatever surgery is necessary to make possible the local instillation of penicillin into the involved joint

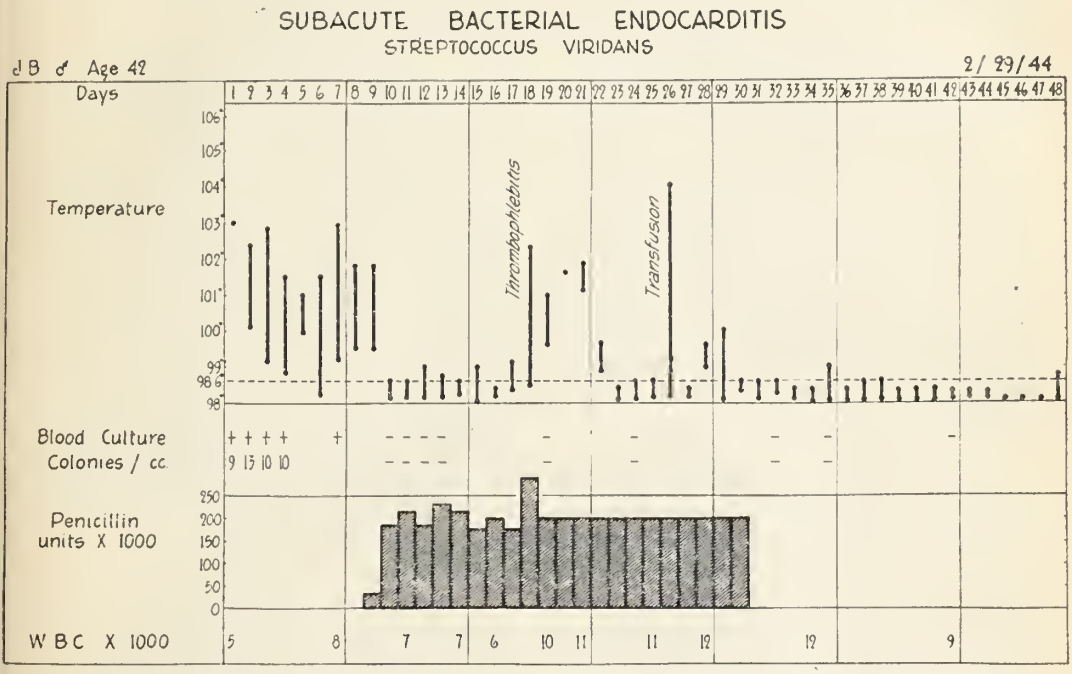


FIG. I. Chart illustrating the clinical arrest of a patient with subacute bacterial endocarditis. The blood was promptly cleared of organisms; the temperature returned to normal within 72 hours after penicillin was begun. Thrombophlebitis and blood transfusions were followed by fever.

### ACUTE OSTEOMYELITIS

Evidence is now accumulating that acute osteomyelitis can be treated satisfactorily without surgical intervention when the therapy is started early in the course of the disease and before abscesses of the soft parts or extension of the infections of the joints has occurred. Penicillin must be given in amounts varying from 120,000 to 250,000 units a day and continued for a period of 2 to three weeks until all clinical symptoms and signs of infection have disappeared. Since there is a lag between the clinical signs of infection and the development of definite roentgenological changes in the bone, one is not surprised to find that destruction of the bone is observed some time after all signs of infection have disappeared. Under these conditions, the lesions in the bone frequently recalcify and complete healing takes place without incision and drainage.

When the infection has spread into a neighboring joint, it is desirable to perform whatever surgery is necessary to make possible the local instillation of penicillin into the involved joint at least once or twice a day. In all cases of acute osteomyelitis in which recovery has taken place without surgical treatment, the patient should be followed carefully over a period of several months in order to be certain that relapses or recurrences do not occur. In a few cases it may be necessary to drain local abscesses in bone some weeks after the acute infection has subsided. In occasional cases that have been treated very early, no signs of bone destruction have ever developed in the roentgenograms.

The treatment of osteomyelitis of the facial bones with penicillin has been followed by excellent results, as reported by Kirby and Hepp (5). When sequestra were present, surgical treatment in addition to the use of penicillin, was necessary to effect complete recovery.

In the case of chronic, hematogenous and traumatic osteomyelitis, Anderson, Howard, and Rammelkamp (6) have found that when sequestra are present it is necessary to remove them surgically in order to obtain satisfactory healing. These physicians were able to report an arrest of the disease with the disappearance of all local and constitutional signs of active infection in 70 per cent of their patients with chronic osteomyelitis. Prolonged treatment varying from 2 to 6 weeks was found to be necessary in order to obtain the best results. Treatment has to be repeated when relapses occur. Primary closure of wounds after sequestrectomy, together with the local administration of penicillin greatly shortens the recovery period. In brief, the treatment of acute and chronic osteomyelitis should be designed to control the infection as rapidly as possible. If dead or necrotic tissue is present, or if abscesses in the soft parts or in the joints have appeared, it is necessary to use good surgical management as well as penicillin if the best results are to be obtained.

### Infections Due to Clostridia

*Gas Gangrene.* The best results in the treatment of gas gangrene follow the use of antitoxin, penicillin, and surgical removal of all necrotic and damaged tissue. If gas gangrene tends to develop in patients who have had injuries to the bone and soft parts with an interruption of the blood supply to the affected part, it is only natural that a certain number of patients will not respond to any form of treatment unless all of the ischemic and damaged tissue has been removed. Jeffrey and Thomson (7), in a study of 33 cases of gas gangrene treated with penicillin, reported a fatality rate of 36.4 per cent. They emphasize, as has already been remarked, that adequate surgical removal of all necrotic and devitalized tissue is the most essential of therapeutic procedures in the management of gas gangrene. Five of their patients were seen late in the disease when surgical treatment was not possible. All of these patients died in spite of intensive treatment with penicillin. These physicians recommend a dosage of 15,000 units every 3 hours for 3 to 4 days for the control of infection in cases in which all the infected tissue can be removed surgically. When this is not possible, it is desirable to continue treatment for 5 to 10 days. They express the opinion that when patients are treated early and adequate surgery is employed, penicillin and antitoxin will reduce the fatality rate in battle casualties to the neighborhood of 20 per cent. Cutler and Sandusky (8) reported their experience with the treatment of 7 patients with gas gangrene, 6 of whom recovered. It is significant that in five of their patients, gas gangrene developed while the patients were receiving prophylactic penicillin therapy. Following the removal of diseased tissue, all of these patients recovered.

### Gonococcic Infections

Of all the organisms that are susceptible to penicillin, the gonococcus is the most sensitive. It is now well established that about 98 per cent of all gonococcic infections of the lower genital tract, either in men or women, can be cured by the administration of a total of 100,000 units of penicillin over a 24-hour period. The remaining two per cent who fail to respond to the first course frequently respond to more intensive and prolonged treatment. No proved cases of penicillin-resistant gonorrhea have yet been encountered.

Gonococcic infections complicated by arthritis, prostatitis, salpingitis, epididymitis, or endocarditis, require much more prolonged treatment. Early and intensive treatment in all of these infections is advisable.

### Syphilis

Following the report of Mahoney and his associates (9) in October, 1943, intensive studies of the treatment of early syphilis, neurosyphilis, and congenital syphilis have been carried out by a group of cooperating clinics reporting to the Penicillin Panel of the Subcommittee on Venereal Diseases of the National Research Council, and cooperating with the Committee on Medical Research of the Office of Scientific Research & Development. Final evaluation of the results will, of course, not be possible for several years. Preliminary reports indicate that a course of 60 injections of 20,000 units each given intramuscularly at 3-hour intervals for 7 and one-half days probably represents the minimum dosage schedule that will be effective in controlling primary and secondary syphilis. In some patients who relapse after this schedule of treatment, more prolonged and intensive treatment may be necessary. Not enough time has elapsed, and too few patients with neurosyphilis have been treated, for a sufficiently long period of time to make any statement concerning the results that might be anticipated. There is some evidence to suggest that the results

in the treatment of neurosyphilis are not as striking as those of early syphilis. Late cutaneous and osseous syphilis apparently respond promptly to penicillin treatment. So far, no reports are available on the action of penicillin in latent syphilis. Some cases of congenital syphilis have been treated in which good early results have been obtained (10). It is agreed by all who are investigating this problem, that penicillin in the treatment of syphilis is still in the stage of preliminary investigation, and no definite schedule of treatment can yet be recommended for routine therapy.

During the treatment of syphilis with penicillin, Herxheimer reactions have occurred with considerable frequency. These are characterized by fever, malaise, headache, intensification of the eruption if one is present, or painful swelling of the primary lesions and the regional lymph nodes. These reactions subside within 24 hours and are not contraindications to continuing treatment.

### Toxic Reactions

It has already been stated that penicillin is a nontoxic drug. There are, however, certain side reactions which may be observed which require comment. So far, no permanent harmful effects on any of the systems of the body have been recorded. About two to five per cent of patients develop urticaria. The urticaria may appear on the first day of treatment, or it may not appear until after treatment has been completed. When it develops, it is commonly seen during the second week of treatment. In a few instances it may be quite severe and extensive, but in most cases it is mild and frequently disappears even though treatment is continued. When penicillin is re-administered at a later date to a patient who has developed urticaria during the previous course of treatment, there may be a reappearance of the eruption. Urticaria is not considered to be a contraindication to continuing treatment or to re-administration of the drug at a later date in most cases. In rare instances it may be advisable to stop treatment, especially if the discomfort is severe.

Occasional attacks of vesicular eruptions have been noted and we have seen one severe rash of this type appearing within 24 hours after the beginning of treatment, especially in areas where there was a severe ringworm infection four years previously.

Pain on intramuscular injection is encountered with varying frequency, depending upon the presence of impurities in the penicillin. The higher the potency of the penicillin, the less local discomfort there may be.

Thrombophlebitis of the veins at the site of injection may occur, especially in patients who are receiving continuous intravenous treatment. Thrombophlebitis is associated in some instances with chills and high fever. When this occurs, it is wise to change from intravenous to intramuscular injections. All preparations of penicillin which are now distributed are tested for the presence of pyrogenic agents. The febrile reactions due to impurities that were occasionally encountered in the early days of developing penicillin, are no longer seen. Drug fever, analogous to that seen in sulfonamide therapy, has not been reported. Occasionally patients may develop low grade fever after the clinical signs of infection have disappeared, and this subsides completely with the discontinuance of penicillin.

Occasional patients will develop abdominal cramps with or without diarrhea following penicillin, and nausea and vomiting have been observed in a few patients. The maximum therapeutic dose of penicillin that can be given safely in man has not yet been determined. It is known that doses as large as 4 million units a day have been given in one or two instances without ill effect.

At present there are no known contraindications to the administration of penicillin, although there may be reason for giving small initial doses to patients with cardiovascular extra-genital syphilis. As far as is known, penicillin is not incompatible with any other drug or article of diet.

### Miscellaneous Infections

A large group of miscellaneous infections have received treatment with penicillin with promising results. In most instances the number of cases so treated has not been large, so that final assessment of its value cannot be made. However, patients with *actinomycosis* have been improved following treatment, and especially those cases in which it is possible to remove infected tissue surgically, or in those instances in which there is a super-infection due to the *Staphylococcus aureus*. *Anthrax*, with or without bacteremia, responds promptly to penicillin, and a few cases of yaws and rat bite fever due to *Streptobacillus moniliformis* have been treated with results suggesting that penicillin is a potent agent in these disorders.

Penicillin is active *in vitro* against *Corynebacterium diphtheriae*; a few cases of clinical diphtheria

have been treated with a combination of antitoxin and penicillin with results that are difficult to evaluate. Penicillin will not replace antitoxin and should not be used in lieu of antitoxin. The supplementing of antitoxin with penicillin in cases of laryngeal diphtheria or diphtheria gravis may prove to be valuable, although the evidence to support this procedure remains to be accumulated. The treatment of diphtheria carriers with penicillin has not met with permanent success.

The position of penicillin in the treatment of chronic paranasal sinusitis, chronic infections of the ears, nose, and throat, remains to be determined. The same is true with gingivitis and stomatitis caused by the Vincent's organism.

### Prophylactic Use of Penicillin

White and associates (11) have demonstrated that when penicillin is administered intramuscularly for one week prior to lobectomy or pneumonectomy and followed by continuation of penicillin treatment after operation, the incidence of postoperative empyema is greatly reduced. Penicillin will perhaps not decrease the number of infections in wounds when it is not combined with adequate surgical treatment.

### Penicillin Failures

No discussion of penicillin would be complete without saying something about the cases in which penicillin fails to influence the course of the disease. The largest group, of course, includes those cases of infection due to micro-organisms which are not susceptible to the action of penicillin such as those listed in Table I.

The next large group are those disorders in which penicillin has been shown to be ineffective as listed in Table II.

In general it can be said that there is a fairly good correlation between the sensitivity of the infecting strain of micro-organism and the clinical amenability to treatment, so that when the treatment appears to fail it may be due to inadequate daily dosage or to treatment of only a few days duration. The treatment may be started too late in the course of an infection, or there may be an overwhelming infection even with a sensitive strain.

In the case of wound infections, penicillin may fail in its function when debridement is incomplete, or when necrotic tissue or foreign bodies are present.

In our experience the development of increased resistance of micro-organisms to penicillin plays little if any role in the failure of infections to respond to its action. While we can demonstrate a change of sensitivity in some strains of *Staphylococcus aureus* during treatment when they are tested *in vitro*, the evidence is far from convincing that this phenomenon plays a dominant role when a regression of signs of infection fails to occur. The reason for this statement is that there are usually other factors present which influence the outcome. This is especially true when the resistance to penicillin increases in organisms in empyema cavities and in chronic osteomyelitis.

In brief, when any patient with an infection due to a susceptible organism fails to show a satisfactory response to penicillin, one should review the dosage, search for signs of a bacterial endocarditis, or an abscess which hasn't been drained.

TABLE I

| |
|---|
| Typhoid—paratyphoid |
| Dysentery |
| E. Coli |
| H. Influenza |
| B. Proteus |
| B. Pyocyaneus |
| Br. Melitensis (undulant fever) |
| P. Tularense (tularemia) |
| B. Friedlander |

TABLE II

| |
|---|
| Tuberculosis |
| Poliomyelitis |
| Hodgkin's disease |
| Histoplasmosis |
| Moniliasis |
| Malaria |
| Cancer |
| Lupus erythematosis diffuse |
| Non-specific iritis & uveitis |
| Pemphigus |
| Toxoplasmosis |
| Blastomycosis |
| Coccidiomycosis |
| Acute rheumatic fever |
| Virus infections |
| Acute & chronic leukemia |
| Ulcerative colitis |
| Infectious mononucleosis |

### *Conclusion*

In conclusion, it can be said that penicillin has exceeded our highest hopes as a chemotherapeutic agent. It is unquestionably the most effective agent for the treatment of many infections. There is no other known chemical that is so powerful against bacteria and so harmless to the host.

All of this is most extraordinary when one appreciates that fifty milligrams will cure the average gonococcic infection, 300 milligrams or less is needed for patients with pneumococcus lobar pneumonia, and 3 to 5 grams will arrest between 50 and 70 per cent of the infections in subacute bacterial endocarditis.

What we need in the future are effective agents for the similar control of gram negative bacillary infections and virus infections.

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# The Cancer Problem As It Stands Today*

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I FIRST express appreciation to the Mütter Museum Committee and to the Council for asking me to deliver this Mütter Lecture. I find, as you can well imagine, that the broad title "The Cancer Problem as it Stands Today" puts considerable responsibility on my judgment as to the topics to be discussed. I hope the choice meets with your approval. Even so, I necessarily broad-jump over many details to pick out generalizations. I shall express my own opinion on various subjects which will be compounded of personal experience and the fortunate situation of having the help and advice of many individuals and groups to whom I express appreciation. I respectfully ask, therefore, that when I express opinions and recommendations you will consider them for what you think they are worth and as of tentative value, to be changed as more facts are accumulated and more relationships are clarified. In this presentation the word cancer means any malignant tumor. Further classification will be given when this is pertinent.

Approximately 165,000 people in the United States will die of cancer in 1944, or one every 3.2 minutes. This estimate is based on the fact that the mortality from cancer has been increasing steadily during recent decades. In 1900 it was eighth or ninth among the leading causes of death. In 1940 it was well to the fore in second place. First place in the list of deaths is occupied by diseases of the circulatory system which, as we know, are composed of many different pathological anatomical findings and a host of etiological factors. It is, therefore, probably no exaggeration to say that the greatest single cause of death is cancer. The conceptions of the word "single" are debatable. Obviously cancer of the lower lip is different in many respects from cancer of the stomach. Nevertheless it is possible to find least common denominators in all cancers, largely depending upon the point of view, whether clinical, experimental, genetic, chemical or others.

As the death rate from cancer rose, there was debate between statisticians of life insurance companies and of official agencies as to whether it was a real or an apparent increase. Today it is fairly well agreed that even after the effect of the increasing proportion of older age groups in the population is compensated, the death rate has shown an increase during the last forty years. For the past two or three years there have been indications that the rate of increase is slowing down. Apparently this is due not to a decrease in the number of potential cases but rather to the relative decrease in the rates of population increase in later years. Other facts, no doubt, have contributed to the increased recording of cancer deaths. For instance, diagnostic facilities and acumen have been increased and thus, perhaps, many deaths now attributed to cancer would have been otherwise classified in the earlier years. I say "perhaps", because such figures are futile. How can we know what would have happened twenty, thirty and forty years ago if the diagnostic acumen had been as good as we flatter ourselves into thinking it is today? If it gives us any pleasure and satisfaction to project ourselves back into the past and speculate on what might have happened had we been as smart then as we are today, it appears just as legitimate to guess what the figures would be today if we were as smart as we ought to be, let alone what might be recorded in the future. For this remark I allude, among other factors, to methods of diagnosis.

The number of tests proposed for cancer no doubt runs into the hundreds. To classify a few; there are those depending on the agglutination of cancer cells in vitro or the precipitation of alleged cancer products from blood, urine or other fluids or tissues; there are skin "allergy" reactions; the observation of crystalline patterns (I almost said crystal gazing) with copper sulphate, zinc acetate and various other substances mixed with blood,

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urine or other fluids from suspected cancer cases; but not one of them has proved as accurate in differential diagnosis as a thorough history and physical examination, which have their own errors—the earlier the cancer the larger the margin of error in diagnosis. There remains, outside of obvious spread and metastases, as the only method of settling the diagnosis the microscopic picture. A properly chosen bit of tissue fixed immediately, carefully stained and examined by a competent pathologist should be diagnosable with a margin of error of less than 3%. This error is certainly small considering the complications involved. While on this subject I submit the following thoughts.

It is a universal practice, and a good one at that with limitations, to send slides of doubtful cases to a number of different pathologists. When different words are used for diagnosis the tendency is for the surgeon, for instance, to accent this phase, often with a smirk of satisfaction. It is my experience that in 95% to 97% of cases the differences of opinion are of words and not of things. To make this clear I submit that in these doubtful cases there is usually a difference of opinion among pathologists not on the crucial point of whether or not the tissue is a tumor but rather on what name to attach to it. I recommend, therefore, that more attention be paid to the classification—tumor—as distinguished from inflammation, degeneration and other pathological processes, and whether or not it is malignant. I could devote considerable time to a discussion of "the confusion of tongues" in the nomenclature, but only state that it is high time that many of the names of tumors be put in the category of historical relics. An attempt was made some few years ago, when the Division of Cancer Control of the State Department of Health was in existence, to have a committee composed of surgeons, roentgenologists, pathologists and others interested to attempt clarification of names, at least in Pennsylvania. I recommend that this be taken up again if and when it is possible.

If pathological examination is the court of final appeal in diagnosis, it is interesting to note that the percentage of reported cases of cancer with the diagnosis confirmed by microscopic examination of the primary site and region is about 65% according to Dorn's studies. If the Division of Cancer Control in the Department of Health, during its brief existence from 1939 to 1941, did nothing else it increased the number of biopsies in Pennsylvania from about 50% to 70% of the cases reported. Of course, it is not necessary to have microscopic confirmation of, let us say, cancer of the breast when the tumor is bigger than an orange, is ulcerated, adherent to the chest wall, the axilla full of hard nodules, the patient is pale yellow in color, is short of breath, coughs, and has pain in the back but it is necessary, in fact essential, in cases about which we hear so much exhortation, namely, early cases.

I, personally, rejoice when I see patients with a little granularity of their cervices, or a tiny lump in their breasts hard to find, or a tiny fissure in their lower lips. Then when they ask "Is it Cancer?" I can truthfully tell them that I do not know, but that a biopsy is necessary to settle the case. The objection that performing a biopsy tends to spread a tumor has been disposed of by a number of studies both in human beings and in mice. But the biopsy must be performed with delicacy of technic and proper choice of instruments and methods for the various sites. Certainly there is much less danger of spread from a properly performed biopsy than from rough handling and squeezing of tumors in an attempt at physical examination of them. I strongly recommend light palpation and not massage in diagnosis. I shudder at the practice I have seen in certain tumor clinics of having the attending physicians forming in lines like a parade to squeeze a lump in the breast.

The diagnosis of cancer in the majority of cases is made on the topographical microscopical anatomy and not on cellular details. It brings to mind the famous adage of Professor Warthin that "A good pathologist requires a low power lens and a high power brain." Exceptions to this are found in certain individuals who have been particularly schooled in cellular diagnosis of material from particular places. Thus Papanicolaou, Meigs and others with much experience are able to make the diagnosis of carcinoma of the uterus from properly prepared smears. I would urge, however, that this method be used as a diagnostic criterion only when considerable experience has been acquired with both normal and pathological states.

Needle and punch biopsies, in my experience, are also limited in their application, for just as in cervical smears, a special experience is required. When the diagnosis of cancer can be made positively on punch biopsy or aspiration material the

results are unequivocal. When the results are negative they certainly do not exclude malignancy. I would urge limitation of punch and needle biopsies to certain specific types of cases. Never do I advise punching a hole into a breast tumor but recommend that the patient be taken to the operating room, the lump removed, examined then and there by frozen section, and base further treatment on the immediate findings. The same procedure is recommended for tiny lesions of the lower lip, of the cervix and of the skin. Take the whole area and a bit of the surrounding tissue for a study of its topographical microscopical anatomy.

While on this subject a further word about topographical microscopical anatomy is in order. For many years we have drawn a sketch of the area to be excised, let us say, of the skin of the face, marking it for future identification. When the tissue is removed, not one block is taken for pathological examination but the entire edges of the excised piece are sectioned, and a rough reconstruction of the tumor is made. Then if it is found that the surgeon has cut through tumor tissue in any particular area he can further excise the tissue in this area whereupon the same procedure is followed. While it is true that the spread of carcinoma is often discontinuous, nevertheless, by this method an increased percentage of complete excisions can be obtained. For an elaboration I refer you to the work of Mohs who uses zinc salts as fixatives during operation and keeps excising until no more tumor is visible.

As an addition to the figures first given, it is safe to estimate four living cases for every death. Thus in the United States there are approximately 650,000 individuals with cancer at this moment. If we estimate conservatively that each case costs $500 per year for care, the bill for the United States is about $350,000,000 per year. If we add economic loss, for families are often disrupted by cancer, the total cost is at least one billion dollars a year. This is one phase of the cancer problem as it stands today.

But to begin more general considerations. It is a fact that cancer may arise in any and all parts of the human body and from all sorts of tissue. It is also a fact that cancer is frequently found in lower animals even though systematic searches for it in these animals are rare. Thus tumors occur in mammals, birds, amphibians, reptiles, fish and in various invertebrates, until we are almost justified in stating that they may arise in any multicellular organism. Mottram even asserts that carcinogens produce changes in unicellular organisms (Paramecia) leading to behavior and morphology comparable to that of cancer cells. In the case of plants the debate is not whether uncontrolled proliferation and improper differentiation of cells occur but whether or not to call them tumors—malignant or otherwise. Many interesting facts have been discovered in the study of plant growths, some of them highly suggestive. I should like to discuss them further but can only refer you to the work, for instance, of A. J. Riker of Wisconsin and Philip White of the Rockefeller Institute in Princeton for their results, as well as their reviews of the literature.

If the above is true, namely, that cancer arises in all tissues and in many, if not most, multicellular organisms, it is a fact that the possibility of development of cancer is a potency of all organisms and all tissues. Herein are many opportunities for finding the least common denominators characterizing cancer tissue wherever it may be found.

The broad biological question can be posed in this fashion; how is it that normal cells grow into definite patterns and how do the patterns come to be disturbed when malignancy appears? Immediately we plunge into some of the profoundest questions concerning living things and their activities. That there is ORDER in developmental patterns has been recognized from time immemorial and pondering on this ORDER has led many of the great biologists of all times to become philosophers. But philosophy fell into disrepute, especially during the nineteenth century. The reasons are not far to seek, for the mixing of metaphysics and science in the minds of many who style themselves philosophers results only in confusion and at times downright nonsense. Philosophy can, however, be used as a powerful intellectual tool for the construction of syntheses if handled for this purpose and for the added one of constructing theories and hypotheses upon which experiments can be conducted. For those who still have a horror of philosophy and shudder at its name, I recommend, among others, Whitehead and his "Science and the Modern World," and Pareto's "The Mind and Society." By no means neglect Lawrence J. Henderson's "The Fitness of the Environment." To those who do

experiments on a hit or miss method, and many such are performed, these and other books will supply leaven to the dough. The cancer problem particularly needs synthesis for there is hardly a subdivision of science from which information does not come. Cancer, baldly stated, integrates into the problems of growth and development and synthesis is necessary for intellectual integration. Whether we call it philosophy or not is again a matter of names.

In studying growth and development we may begin at many points, but for convenience the fertilized ovum may be chosen. Not that growth and development do not start earlier, for both ovum and spermatozoan are highly differentiated. Their development may be regarded as multiplication and differentiation wherein the highly important reduction of chromosomes takes place and finally, separation of the mature cells. Fertilization is not necessary for the development of competent organisms, for all ova, in which the experimental difficulties have been conquered, have been found able to develop without aid of spermatozoa. Fatherless rabbits are well known and the human ovum itself has divided at least once parthenogenetically in the laboratory. Spermatozoa, also, from several species have developed in eggs from which the female nucleus has been removed. The experimental conditions under which this takes place are more difficult to achieve than in the case of ova but the androgenetic frog is well known. This is of interest in the theory of the development of certain tumors, such as teratomas and dermoids, which, hypothetically at least, may have their origin in parthenogenetically developed ova or spermatozoa (Bosaeus). Other similar tumors may come from the unfortunate ones of twins, triplets, quadruplets and perhaps even quintuplets.

But development in higher animals proceeds ordinarily from a fertilized ovum. The processes by which a fertilized ovum develops into a new and competent individual are many and varied. For our purposes we may concentrate on three: (1) multiplication, which occurs by way of mitosis, the general morphologic details of which are similar in all species of animals and plants; (2) the second process we may call differentiation, defining this term by stating that it is a series of changes whereby cells become more specific from more general, wherein they come to take on different compositions in tune with the functions which they perform in the development and maintenance of the organism; (3) the third process we may call organization and it is especially this term which must be defined carefully. For our purposes let us say that organization is that series of processes whereby cells of different differentiations gather themselves together in the right numbers, at the right times and the right places to produce organs and parts which function within the frame of a new individual with the characteristics of the lineage from which the original fertilized ovum came. You will note that I say "within the frame" of an individual. This concept—frame of an individual—is best treated in a philosophical way, specifically by the so-called "organismal" theory. The cell theory in its classical form is no longer a generalization but describes special cases. There are numerous competent organisms with nuclei but no cell walls, for instance, the siphonaceous algae. If we think of protoplasm as continuous within an organism, then its division into cells is one of its differentiations. Thus it is better to speak of the activity of protoplasm than the activity of cells in many cases. As deBarry put it "the plant (animal) builds cells and not cells the plant (animal)." Certain tumors are composed of nucleated masses of protoplasm, i.e., syncytiae.

From this point of view an examination of cancer shows that its cells multiply but not within the frame of an organism, i.e., they do not organize at all in the sense in which this word has been used. Furthermore there is something wrong with the way cancer cells differentiate, not that they do not reach high degrees of specialization, for many times they do, but there is always something wrong and they are not under the control of the organism as a whole. "Cancer is an escape from the individuation field" (Needham).

According to the theories of evolution multicellular animals arose probably not by the union of separated cells but by their division without subsequent separation. As the number of cells in a mass increased those in the center of the group no longer were in contact with their immediate environment. They thus depended upon the cells surrounding them and in contact with the environment for their nutrition and for excretion of their waste products. This inevitably led to specialization which is another term for differentiation. It may be visualized that finally the cells specializing in nutrition or excretion were gathered together

in groups, thus "organizing." Carrying these interesting but perhaps futile speculations further one might say that the last to develop would be the first to go when anything goes wrong. This is what actually occurs in cancer: organization goes completely, differentiation less so and multiplication remains. Perhaps these speculations are futile but on the other hand they perform the useful purpose of concentrating attention on the organization problem and the differentiation processes. We have occasion to emphasize this a number of times. We state that just as a century or more ago comparative anatomy was the central problem of biology, in the middle of the last century, evolution, and the beginning of this century, chromosomes, so at the present time the central problem of all biology is this very organization problem. How is it that morphogenesis occurs so that organisms breed true and do not, for example, mix up the front leg of a giraffe with the hind leg of an ostrich on the body of a human being? If cancer represents, from this point of view, absence of organization, we readily see that the above speculations may be of value in concentrating attention on this phase of the subject and this is another place in which the cancer problem stands today.

A few detailed remarks upon these three processes are now in order. It has been shown very clearly that anatomically, genetically, chemically and physically, while interdependent, they are, nevertheless, separable phenomena.

An enormous amount of work has revealed no differences characteristic of cancer in the anatomical details of cell division. Testimony is given in some fifteen hundred publications in which some of the most able workers have participated. True enough, in the tissues of cancer, multi-polar mitoses and various kinds of distortions have been found, but so also are they found in growths other than cancer. Furthermore, the central parts of cancerous masses are known to be in precarious health. Therefore, for purposes of comparison the healthy growing edges of a tumor must be compared. It will be found that many of the announcements of characteristic changes in mitotic processes come from studies made on only questionably viable cancer cells.

Multiplication per se is not a cause of differentiation in normal cells for differentiation takes place in many instances without multiplication. Therefore we should hesitate to attach the blame for the improper differentiation of cancer cells on multiplication. Cancer is not a disease of cell multiplication—unless future evidence decides otherwise.

While multiplication, differentiation and organization, as stated, are independent and serve different functions, nevertheless, there are interrelations. Cells cannot differentiate unless they are there and they arrive by multiplication. They cannot organize unless and until they have differentiated. The relationship may be expressed this way:

Cells multiply
Cells differentiate after they have multiplied
Cells organize after they have multiplied and differentiated

By substituting a few words the following results:

Cells multiply
Cells differentiate because they have multiplied
Cells organize because they have multiplied and differentiated

or it can be stated in this wise:

Cells multiply in order to differentiate
Cells differentiate in order to organize

or:

Cells differentiate and organize because they have multiplied.

The final touch to this semantic legerdemain is the following statement:

Cells multiply because they do not differentiate and organize. Is this the "cause" of cancer?

You will recognize this immediately as the long sought "cause" of cancer. Cancer cells continue to multiply because they do not differentiate properly and do not organize at all! Again our attention is centered on the organization problem.

Perhaps you do not approve of what I have called "semantic legerdemain," but it is analogous to the use of ordinary mathematics—nothing more comes out of juggling figures than is put in, but ofttimes by rearrangement, mathematical statements are put into more intelligible, more useful and more investigatable form. That this is also a justifiable method of the use of words instead of mathematical symbols is amply evidenced by recent studies in what is called "symbolic logic" as exemplified, for instance, in J. H. Woodger's "The Axiomatic Method in Biology." There is no time for further discussion of this most interesting recent development of a very old subject except to say that its use in expert hands tells us what we know and what perhaps is more impor-

tant, what we do not know and that in unmistakable terms. But perhaps I had better justify a few of the legerdemain statements before proceeding further.

A main point is that differentiation is antagonistic to multiplication. Every text book of biology bristles with facts supporting this statement. Actually there is even a chemical reason why cells which pass a certain stage of differentiation can no longer divide. In passing from the undifferentiated to the differentiated state there is chemical reconstitution, and the complicated chemical dynamics necessary to mitosis cannot take place after the differentiating chemical changes have occurred.

You will note in the multiplication-differentiation antagonism our old friend "histological tumor grading." The place this occupies today is a minimal one and as I had occasion to emphasize years ago, it should play no part in clinical tumor practice.

One more elaboration in regard to differentiation. It is a determined fact that within undifferentiated tissues there are more chemical compounds with unpaired electrons than in differentiated tissue. Many compounds are of such nature that different syntheses can be effected, for instance, of the amino acids. Now if a cell passes from the undifferentiated to the differentiated state and turns into, let us say, muscle, it acquires definite chemical moieties—in this case myoprotein. Which it did depended upon the environment, broadly speaking, in which it found itself. In biological terms, the potency of a cell is greater than its developmental fate. It can do more than it does. Which of its various possibilities it picks out depends upon its environment. There is a point at which it is determined what path of differentiation a cell shall take. As it proceeds there is no turning back and after certain degrees of differentiation have been reached de-differentiation of a single cell is no longer possible.

If we translate these remarks we find that cancer cannot arise from cells which have reached a certain degree of differentiation. All cancers must arise from division-capable cells—hence incompletely differentiated. If the cells from which cancer arises are incompletely differentiated then their developmental possibilities should be greater than their developmental fate. Experience shows that they are, for various parts of many tumors show different anatomical pictures indicative of different degrees and kinds of differentiation. Hence the standard methods in most text books, and in most teaching, of explaining the origin of tumors, have an element of incorrectness as based on present day biological knowledge. As a concrete example we should not say that a squamous cell carcinoma arises from squamous cells for squamous cells have differentiated beyond the point where they can divide. The proper method of statement is: the spinous-cell or squamous-cell carcinoma arose from incompletely differentiated cells, that is, from basal cells. They differentiated to look like squamous cells but are never quite identical with the normal. Disturbance of the differentiation processes, not in degree but in kind, is one of the characteristics of malignancy.

*Organization:* Normal development is epigenetic and not pre-formed. One part in developing brings to bear its influence on the parts succeeding. Only a few of the influences which guide organismal growth can be mentioned and fewer still will be picked to examine their relation to cancer. Among them are genetic factors, hormones, growth centers, gradients. It is repeated that cancers do not organize at all in the sense in which the word "organization" was defined. That cancers influence normal tissues to grow with them is evident from the growth of stroma in them. The cancer stimulates stroma if only to provide nutrition. But the cancer in its turn is not influenced by organizing influences as is normal tissue. Cancer is a disease of organization.

*Hormones:* Insofar as their effect on growth and development is concerned, hormones have been evolved to guide differential growth. They add nothing and subtract nothing from the potencies inherent in cells. They play upon them, now allowing them to expand, now contracting them. The surge of activity of the gonads both before and during puberty allows the cells of certain organs to express more of the potency present in them, leading to a change in the differential contour of the body. As a pathological example the large head, hands and feet of acromegaly may be mentioned, or the benign tumor or cysts of the breast with granulosa cell tumors of the ovary.

Direct experiments with hormones on the malignancy problem have been done in great numbers with all the various kinds in both addition and subtraction experiments. The sex hormones, for example, produce a series of changes classified as metaplasia. Squamous cells replace the cylin-

drical cells lining the prostate glands. Squamous cells replace the lining of the uterus. Male mice develop breasts as large as those of their sisters. Whether or not the injection of hormones directly "causes" cancer depends upon the definition of the word "cause." They certainly increase the incidence of cancer of the breast in mice—but, may I say, only in strains predisposed to the development of the disease? All in all, perhaps we may generalize by stating that of and by themselves hormones do not directly produce cancer. This statement will be debated but it can be resolved into the following analogous situation. Of a hundred traditional Irishmen, all smoking short-stemmed clay pipes, several will probably develop cancer of the lower lip. Why not all? Something in addition to the hot clay pipe stem is needed and apparently this is true of the hormones. If it is postulated that the "something else" is constitutional, then it may well come under the heading of genetics.

The extremely practical question of whether the use of female sex hormones in women predisposes to the development of cancer is unanswerable at present. The amount of hormones given clinically is usually much less than that given experimentally to mice. We cannot as yet pre-determine by any methods which of a strain of animals or human beings is susceptible to cancer. If hormones cause cellular activity in the breast or uterus of a woman there is more statistical chance of cells undergoing malignant change when a thousand are active than when only ten are active. At present it would appear advisable to make physical examinations of breasts and uteri at frequent intervals in women given female sex hormones.

Another question—what influence do hormones have on cancer already established?—has a better answer. They have no direct effect on cancer cell multiplication as evidenced thus far. Castration of males for relief of carcinoma of the prostate and its metastases acts by way of the differentiation of the cells of the tumor and not of cell division.

On the other hand certain cancers produce hormones—thus testicular tumors, adrenal tumors, thyroid tumors, pituitary tumors and others. The background biological process comes under the heading of "chemical differentiation of cells" by which is meant that many cells build tiny laboratories within themselves which produce highly specific and characteristic substances. In the so-called hormone-producing tumors, the products of their intracellular laboratories manifest themselves by changes in the sex organs, in the psyche, in differential growth, in intermittent hypertension and various other phenomena. So characteristic are the symptoms that the presence of such tumors can be diagnosed at times over the telephone!

*Genetics:* Cancer as such is, of course, not hereditary. It is the predisposition to the development of the disease that has been shown to have a genetic background.

Theoretically we may classify the genetic phase of the problem into three groups.

1. We have stressed that the practical difference between cancer cells and normal cells is loss of the ability to organize of the former and their inability to differentiate normally. These two characteristics I call "practical," because they are the basis of diagnostic procedures. Since they are transmitted from cell to cell, they have been said to constitute a new race of cells, or that "somatic mutation" has occurred in a normal cell. This brings up the concept of "somatic mutation" as it occurs in all biology. The major enigma is to differentiate changes in the cytoplasm and the nucleus, and to assess the relative proportions of each. There is abundant evidence that chromosomal or genic changes occur in somatic cells. However, quite recent work has shown that self-reproducing bodies in the cytoplasm also may change or mutate and, what is especially significant, under the control of the nucleus. Haddow stresses Sonneborn's work in protozoa and studies of the mutations of plastids in plants. As an example from plant physiology, we mention that self-reproducing bodies in the cytoplasm depend on the nature of the nucleus;—in the so-called Japonica mutant of maize, the white stripes in the leaves are due to a mutation of the plastids which is conditioned by a particular recessive gene in the nucleus. The maize plastid loses one of its capacities to differentiate—in this case to make chlorophyl. We may say, therefore, in the case of the transformation of a normal to a cancer cell that the concept "somatic mutation" is legitimate, reserving for the future the determination of the relative importance of the nuclear and cytoplasmic constituents in this transformation. In any case it is clear that cytoplasmic mutation is important in cancer for viruses grow in the cytoplasm of

preferred cells, the descendants of which are altered.

2. The second problem concerns the genetic constitution under which the predisposition to the development of cancer occurs. It is well known that mice can be so bred that the susceptibility to cancer is increased or decreased. Further facts are that the inheritance of each type of tumor is different and specific. In this intricate situation the development of the specific tissue patterns, for example, of carcinoma of the breast in mice, is similar to other genic effects such as size differences or resistance to disease, in which the conditions are sometimes simple and sometimes extremely complex. The predisposition to cancer in mice is not dominant nor a simple recessive, indeed in certain strains of mice breast tumors are not chromosomal but perhaps cytoplasmic in their inheritance.

In human beings the evidence is by no means so clear cut for reasons which are obvious. Human beings do not mate to please geneticists and most human beings do not know what killed their grandfathers or grandmothers. Human evidence comes partly from so-called cancer families in which a large number of the members develop the disease. A second source of evidence comes from twins in which case monozygotic twins yield a probability of 90% and dizygotic, 30% to 35%. There are many cases in the literature of identical twins who developed, for example, carcinoma of the same breast, in the same position, within a few months of each other. Further evidence is given in the work, particularly, of Madge Macklin which shows how statistically improbable the development of cancer is in many instances unless there is a genetic basis.

It is quite apparent that the theory of "chronic irritation" has occupied not only the center, but almost the entire stage for so long that the hereditary factors have been neglected. This is readily understandable, especially on the part of clinicians, some of whom are ready to accept the theory of "chronic irritation" as an established fact because they have witnessed an occasional tumor developing in the site of chronic irritation. This is not to decry the removal of foci of irritation such as infected cervices, leg ulcers and a host of others but at least the mental reservation should be made that the direct relationship to cancer has no rigid proof as a generalization. This does not exclude "chronic irritation" as a selector of susceptibles but rather puts it in the proper perspective. There are plenty of other reasons for removing foci of infection.

Reluctance to accept an hereditary basis in human beings is understandable also for there is nothing we can do about choosing our grandparents and thus avoiding the susceptibility and there is much that can be done about "chronic irritation."

In generalizing we may say that there is a genetic predisposition to the development of cancer in many strains of human beings, that it is not for cancer in general but for cancer of a specific organ or part. As a recommendation, people who come from cancer families should be examined more frequently perhaps than others. The problem of trying to determine which human beings have hereditary susceptibility has no answer at present but this is true for all sorts of other skeletons in the human closet, except in a few instances on a probability basis.

3. For completeness, the third division of genetics in cancer concerns transplantation. It is possible to so breed mice that they will become more susceptible or less susceptible to transplantation of a particular tumor from within the same species. It is a matter of selecting the compatibility of host and transplant. In some cases it is identical with antigenic properties. When a strain of mice has been so bred that it will "take" a particular tumor it does not necessarily "take" others. The larger problem in this field is the transplantation of tissues in general. The fact that skin, let us say, from A cannot be transplanted to patient B prevents the establishment of "skin banks" analogous to the successful establishment of blood banks.

A constitutional or genetic susceptibility is also displayed to carcinogens by various strains.

*Carcinogens:* The carcinogen story usually begins with chimney sweeps' cancer and soot as recorded by Percival Potts in 1775. Many attempts to reproduce cancer in animals with soots and tars led finally to its experimental production in 1915 by Yamagiwa and Itchikawa. Woglom's publication of 1926 gives 290 references; some 400 were added from 1926 to 1932 and several hundred more from 1932 to the present. The following generalizations are applicable at present. Carcinogens produce malignancy readily in certain animals, such as rabbits, mice and rats. Others, such as guinea pigs, are relatively

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refractory. That the production of cancer is not entirely local is shown by the fact that strains of mice may be so inbred that they become more susceptible indicating that a general genetic factor is involved. Neither age nor sex is important. The time factor is the same for young or old animals. Some carcinogens are more potent than others. Carcinogens start malignancy but are not necessary for its continuance. Many need not be applied more than a few times when months later malignancy appears in the area treated. This is analogous to the latent period in development of aniline bladder cancer in human beings. The transformation from distortion to actual malignancy is sudden. This latter statement will be debated. It is interesting that in the animals which are refractory to carcinogens, e.g., guinea pigs, the application of carcinogenic compounds such as potent tars produce all the changes which we are accustomed to think of as precancerous but the animals do not develop cancer. Therein is a lesson in the diagnosis of "precancerous" in human beings. Such a diagnosis implies a prophecy and scientifically we should be cautious. Practically we may say to a group of one hundred human beings with, e.g., hyperkeratoses "some of you will develop cancer in those blemishes. I cannot tell which but if all of you have all the lesions removed none of you will develop cancer."

Almost three hundred compounds are listed as active carcinogens. Most of them produce their results by direct contact on the skin, under the skin, or in other situations; but certain ones, such as ortho-amido-azo-toluol pick out specific organs, i.e., the liver, when fed by mouth, but are under dietary control since at least biotin favors and riboflavin antagonizes the carcinogenic activity of these compounds. No generalizations are possible at present as to chemical structure. They do not all contain carbon, for arsenic and zinc chloride are known to produce cancer; and so do the physical agents, X-rays and ultra violet radiation.

A prime question is the relation of the carcinogens to naturally-occurring metabolic products. Are any of them naturally-occurring? If so then a natural "Cause" of cancer has been discovered. Among them are the cholesterol series. Another is methyl cholanthrene. On paper the relation of numerous degradation products can be constructed but that the necessary chemical reactions actually occur in the human body remains to be demonstrated.

It is obvious that any and all of the carcinogens, to satisfy biological requirements, must somehow change the internal mechanism of cells so that a new race is produced which transmits its altered characteristics. Of what these intracellular chemical and physical changes are, not one bit of settled knowledge is at hand. As a matter of fact we know too little of normal intracellular dynamics for any comparison of any kind to be made.

*Viruses:* Viruses are known to produce (1) chicken sarcomas, (2) papillomas in wild rabbits and cancers in tame rabbits, (3) frog cancers, and (4) possible mammary tumors in mice since there are indications that the "milk agent" has the properties of a virus. Are some human tumors virus caused? Perhaps certain warts or condylomas are; for instance, those on the fingers, popularly supposed to be due to handling toads. Some plantar warts are known to occur in epidemics spread from gymnasium floors, shower baths, etc. Viruses and tumors have been the subject of presentations in Philadelphia on several occasions and interesting though the subject is we must hurry on.

Very little has been said in Philadelphia about bacterial products and cancer, so a word or two may be in order. Beginning in 1866, observations have multiplied to the effect that a severe attack of erysipelas in a patient with advanced cancer, particularly sarcoma, is followed at times by complete and permanent regression and disappearance of the tumor. William B. Coley observed this when he was a resident in the Presbyterian Hospital in New York about 1896. During the rest of his life he constantly studied the effects of bacterial products on cancer. That Coley's fluid is well known and is the only "treatment" of cancer, particularly sarcoma, which has persistently been used now almost fifty years, and that there are a number of cases that have been cured of sarcoma by the use of Coley's fluid admits of no doubt. In a private communication, Dr. Coley's daughter tells me that six hundred authenticated cases have been collected. No doubt thousands of cases have been treated by Coley's fluid not only in this country but abroad as well. Why haven't more successes been recorded? It is only lately that possible reasons for non-success have appeared. Overheating the material is known to reduce or de-

stroy its potency; filtration through porcelain reduces or abolishes activity. There were no known methods of testing potency until the cultivation of mouse sarcoma (S37) provided this tool. Shear, in fractionating Coley's toxins, has obtained a complex polysaccharide which produces hemorrhage and necrosis in mouse sarcoma and not in other tissues of the animal. It is highly toxic and dosage must be carefully adjusted. Schwartzman has added some information but probably the hemorrhage and necrosis are not an ordinary so-called Schwartzman phenomenon for they occur without previous sensitization. Certain other facts are available. For literature you are referred to Murray J. Shear's publications. We may regard this work at least as a lead. If nothing further of definitive clinical value comes from work in this direction it will undoubtedly add to our knowledge of the biology and chemistry of tumors.

*Chemistry:* I might detail considerable about chemistry and cancer. Beyond calling your attention to the facts that there is a chemistry of the body of cancer-bearing animals and human beings, a chemistry of tumor cells themselves, a dynamic chemistry and physics of normal and cancer cells in which the key subject is intracellular metabolism and various other chemical considerations, I merely call your attention to a publication in which this aspect is well treated. If we agree that control of natural phenomena is obtained not by descriptive knowledge of statics but by knowledge of the more general chemical and physical facts it will be agreed that the more we know of the chemistry and physics of malignancy the more likely we are to obtain control.

It is interesting that in addition to the therapeutic lead with Coley's toxins a number of others stare us in the face, thus with colchicine, various dyes, certain arsenic compounds. Exploration of the possibilities of these, without mentioning others, needs a veritable army and where, oh where, are we to obtain an army for cancer research?

*Teaching of Oncology:* As we have threaded our way through the labyrinth of cancer lore we have had time to stop only occasionally at some way stations. An important one which we now reach is the teaching of oncology. As far as I know there is but one Department of Oncology organized as a department with compulsory courses for medical students in the country today. The late beloved James Ewing was Professor of Oncology in Cornell Medical School but he had an elective course. I realize that the teaching of a disease such as neoplasia in a separate department is a departure from the usual systemic, or anatomic departments such as otolaryngology, ophthalmology, etc. Oncology must be a vertical rather than a horizontal type of course for it cuts through all specialties. That such courses can be organized has been amply shown in Philadelphia. That the organization of such a department can be integrated into others is also amply shown. That the importance of the subject, its high death rate, justify special treatment also seems plausible. Before the war numerous inquiries about the organization of such a course led to the fond hope that similar departments would be organized in other medical schools. Possibly they will be established after the war. For details of how the course is run I refer you to the publications which I have made. I here express my appreciation to the executives and to the staff of Hahnemann Medical School and Hospital for giving me the opportunity of building up such a department, first on an experimental basis, and then as it seemed to prosper on a permanent foundation. I recommend that it be looked into by other medical schools. Not the least advantage is that when our young "accelerated" medical officers return from their war activities they will not have seen much of neoplasms. The more they are taught in medical schools the more able they will be later to cope with this huge problem.

Professional education on a graduate level is continuous. Cancer committees have been appointed in nearly all of the states. The Cancer Commission of the Medical Society of the State of Pennsylvania has been in continuous service since 1909. Efforts take the form of symposia, meetings, discussions and special lectures. For physicians, clinical considerations are stressed but as a recommendation, programs for physicians can be so constructed that a judicious mixture of the background subjects with their clinical implications is present. In the Graduate School of Medicine of the University of Pennsylvania for the past fifteen years there have been given a series of discussions under the general title of "The Relations of Experimental Embryology and Genetics to Clinical Medicine with Special Reference to Neoplastic Diseases." These discussions seem to be appreciated and the student physicians have done

me the honor of attending regularly. As a suggestion, further amplification of such courses throughout the country could be given with profit.

Cancer is presented, mostly in its clinical phases, in meetings of the national societies, such as the American Medical Association, American College of Surgeons, American College of Physicians and the various specialties societies. There is an American Association for Cancer Research and an Association for the Study of Neoplastic Diseases. Years ago, in the former Society, the bulk of the program was made up of presentations of the pathological anatomy of tumors, particularly human tumors. In the latter years this phase of the subject has receded in favor of more physiological and biochemical studies. This is a sign of the times and one of the indications of where the cancer problem stands today.

Before the war there was an international association for the dissemination of cancer information with headquarters in Paris and membership throughout the world. International meetings were held biannually, one of the last ones in Madrid. In September 1939, the last international cancer meeting was held in Atlantic City at which representatives from many countries were present.

An important phase of anti-cancer education is directed toward the lay public. Organized in 1913, the American Society for the Control of Cancer, now called the American Cancer Society, Inc., has engaged in these activities on a country-wide basis. Local groups in many areas have also engaged in anti-cancer propaganda. In Philadelphia, some fifteen years ago, it was difficult to speak of cancer in public places. A persistent campaign has made it possible now to present the subject almost anywhere. For the past thirteen years an annual Cancer Forum has been held in Philadelphia. Interest has steadily increased and in the last years some two thousand attended. The 1944 Forum, held Monday, November 27th, was no exception and as a testimony of the interest of the general public the meeting rooms were crowded for all three sessions. The Women's Auxiliary of the Lankenau Hospital Research Institute, in addition to this and other activities, has held "cancer dances," "cancer bridge parties," "cancer teas," has a Junior Auxiliary calling themselves "tumorettes," all of which has not only raised funds for research and further education but has helped remove the psychological barrier to the very word "cancer." It cannot be emphasized too strongly that the cooperation of intelligent groups of lay people is of the utmost help in acquainting the public with what can be done in alleviating cancer today by the known methods. In this way the "Don't Delay" slogan sinks into the consciousness of many people and the public is realizing that nothing but radical treatment is adequate for present day cure of cancer and is ready to submit without question to this necessity.

A word of caution, however, is not out of place and it is my studied opinion from years of experience in this field that overdoing the propaganda is harmful. The words of Lord Horder describe the situation, "Teach less to the laity than you really know." The tendency to exaggerate to make out a better case should be curbed. Time forbids discussion of the important subject of the education of school children, not only in cancer but in general health matters, with an adequate teaching of biology as a background, but of this I have spoken and written in extenso. It was the Philadelphia County Medical Society which inaugurated the movement culminating in resolutions passed by the American Medical Association, the American College of Surgeons, the American College of Physicians and other national organizations of physicians to the effect that better grounding in science in our school systems will make for more intelligent perception in health conditions, including cancer. I may remark that these resolutions and the help, minimum though it has been up to the present, has been of distinct encouragement to the teachers of science in the high schools throughout the country in their efforts to increase science teaching in public schools.

*Tumor Clinics:* There is no debate at present as to the advisability of consultation between specialists in most cancer patients. This, often done in organized tumor clinics, has been of help not only to the patients but in the general education of the chiefs, residents, internes and nurses of hospital staffs.

To the Tumor Clinics have now been added in Philadelphia and various other parts of the country so-called Health Maintenance—Cancer Prevention Clinics. That these will be of great use in the detection of early cancers admits of no doubt, and this is one of the forward steps in the cancer problem as it stands today.

*Public Health Agencies:* The National Cancer

Institute was established in Bethesda, Maryland, and has been functioning for about five years. Previous to the erection of this building a number of individuals in the U. S. Public Health Service had been assigned to several parts of the country for research in cancer. Thus, a group worked at Harvard, another group in Cincinnati. The workers are now gathered together in Bethesda. The National Cancer Act provides not only for the employment of full-time workers in research but also for the loaning of radium and providing of Fellowships, mostly in clinical or pathological work, in various institutions throughout the country. Much of the research of the National Cancer Institute staff centers around chemistry and cancer but other phases are also under investigation.

One of the unfortunate facts of the cancer problem as it stands today is that several research institutes have been closed and numerous small groups dissipated, sometimes due to the exigencies of war and other times due to lack of funds. There remain, therefore, in the United States but a half dozen or so organized groups for the prosecution of fundamental cancer research. It is one of the ironies of our times that a problem of the magnitude of cancer, which kills and disables so many of our population, should have but a handful of workers engaged in unraveling its fundamentals.

Many state departments of health have Divisions of Cancer Control in their organizations. Pennsylvania had one for two years, from 1939 to 1941, when it was closed at five days' notice. The Cancer Commission of the Medical Society of the State of Pennsylvania hopes that another Division of Cancer Control can be organized within the Department of Health and plans are in the making for presentation at the next session of the State Legislature.

Just what work a Division of Cancer Control in a governmental department of health should undertake is a matter of opinion, which is usually based on the individual's idea of governmental functions in general. The tendency of most legislators, when the cancer problem is mentioned, is to think immediately in terms of a hospital where cancer patients can be treated. As my studied opinion we do not need such a hospital in Pennsylvania, but rather the function of a Division of Cancer Control in the State Department of Health should be a study of cancer as it occurs in Pennsylvania, the rendering of assistance in collecting, classifying and disseminating information, in assisting financially, if necessary, certain institutions not quite able to do the best for their communities. If a large cancer hospital is built and maintained by a State a few very highly trained men are produced and many physicians in the State have a tendency to "let George do it." In the long run it is probably better to develop numbers of centers under private auspices so that larger numbers of competent individuals are trained to handle cancer patients over wide areas. This phase of the cancer problem as it stands today is being hotly debated in many sections of the country.

A phase of the cancer problem in which state departments of health, including our own, can be interested concerns the care of the advanced cancer patient who often is bedridden for long periods of time. Especially at present the burden of nursing care is well nigh insuperable in many families. There are not enough places where such patients can receive adequate attention. In Philadelphia the Visiting Nurse Society is doing yeoman work and several institutions devoted to this phase of cancer are crowded to the doors. Recognition of this problem resulted in an organization in New York for the care of advanced cancer patients in addition to the institutions stemming from the devotion and vision of Rose Hawthorne. The new New York organization, I am told, is amalgamating with the American Cancer Society.

I find in my notes a dozen or more topics, all of which I must necessarily omit, but I cannot close without a word or two about funds for fundamental cancer research. It will be admitted that cancer research is a full-time job, that to teach or practice, and then do a little cancer research on the side is not conducive to the best results. The day of the experimenter with a rabbit in one hand and a hypodermic syringe in the other is about over. To solve problems in cancer requires teams of various specialists. Financial support has been extremely meager—shockingly so when compared with the funds available for industrial research. It is certainly to be hoped that a fresh impetus will be given to cancer research after the war, with at least a reasonable backing in point of time and finance. As a return on their part, workers in cancer must make every effort to organize and plan their work with goals in view and to tackle problems not just because they are "interesting" but because they will

help in the solution of the cancer problem. It is a point of view centering around the idea that the cancer problem needs a better solution than we have today.

I have said nothing about treatment. For the cancer itself there are surgery or irradiation and/or both. Just when the limit seems to have been reached, fresh advances are made. From many fields comes applied knowledge such as better control of infection, blood and plasma transfusions, the physico-chemical equilibrium of the body fluids so that present day surgery of the lung, the stomach, the rectum is far superior to that of just a few years ago. The development of reconstructive surgery makes possible the removal of far larger areas. A few aphorisms describe the situation in part such as "Faint heart ne'er cured cancer patient"; "one surgeon to remove the cancer and its surroundings, another to close the wound"; "no matter how distressing the surgical defect after skillful removal, the cancer will produce a worse defect if not totally removed or destroyed."

We now have a million and even a million and a half volt X-ray machines for deeper penetration and safer skin exposures. It is true that radioactive elements, e.g., phosphorus, have been disappointing in the treatment of cancer, specifically leukemia, but only a beginning has been made. Even so with all the improvements, the gross death rate rises. Sixty per cent of the cancer patients reported to the Division of Cancer Control were dead within one year of definitive treatment. Until better understanding of the fundamentals is reached, and probably even then, the key note is earlier and earlier diagnosis.

Finally I again express appreciation for the opportunity to deliver this rambling story. It is, as you have heard, incomplete in every respect but there is one thing that you may have noticed, viz., a change from the usual pessimism of discourses on cancer of twenty-five or more years ago to healthy optimism, at least from the experimental side. Today, not only are there many main paths of investigation clearly outlined but numerous side lines as well—indeed, some of the main paths are in the form of quite well defined leads. Meanwhile an increasing number of patients with cancer can be placed in a position to be completely relieved of their tumors by wider education and improving technics of diagnosis and removal.

# A Summary of Studies on Immunity in Mumps*

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## *Introduction*

IT IS a somewhat disquieting paradox that among the viruses which attack man least is known concerning those which are responsible for certain of the commonest and most ancient diseases. The properties and behavior of the agents of many relatively rare infections of viral origin are now fairly well defined. But one cannot as yet describe in any satisfactory manner the pathogens of the common cold and of the ubiquitous maladies of childhood: measles, rubella, chicken pox and mumps. In the absence of essential knowledge of these viruses and their requirements for multiplication, analyses of the mechanisms of resistance, which in turn might lead to practicable ways of active immunization, have been greatly impeded. Such general considerations presented a challenge to further investigation.

Of the diseases I have just mentioned, mumps was selected for study. Two facts directed this choice. In the first place, the virus of mumps alone can be transferred with regularity to any of the readily available species of lower animals. That the Macaccus monkey was susceptible to this disease was shown by Johnson and Goodpasture (1) in 1934. Here, then, appeared to be ready at hand the one essential tool for further research.

The military situation during the late summer and autumn of 1941 was the second factor in the selection of mumps for investigation. In the first World War mumps and its complications were responsible for the loss of more hours from duty among our troops than any of the other infections with the exception of the respiratory and venereal diseases. From April 1, 1917 to December 31, 1919 about 4,000,000 man-hours were lost (2). Moreover the severe and painful complication of orchitis was frequent, ranging in incidence from 10 to 25 per cent (2). The mobilization of millions of young men in 1941, many of whom were coming from rural districts where the number of susceptible adults is greater than in urban areas, strongly augured a repetition of the undesirable experience of 1917.

Fortunately this expectation has not been fully realized. So far, outbreaks of the disease have not been so numerous. Although relatively low, however, the incidence of mumps in the armed forces during the present war has not, by any means, been negligible. Since the beginning of hostilities, extensive epidemics have beset several of the large military camps and naval stations in this country and the incidence of orchitis has been as high as 36 per cent (3). Less frequently benign acute lymphocytic meningoencephalitis has also complicated the disease.

In planning our studies it appeared from the practical point of view advisable to direct our efforts toward the following objectives:

1) The development of specific methods of diagnosis which would be of especial value in those cases in which involvement of the salivary glands is absent or questionable.

2) The establishment of a convenient method for determining susceptibility or resistance, since on epidemiological grounds there is evidence which suggests that the disease may occur in an inapparent or silent form.

3) The determination of whether or not it is possible to immunize by means of preparations of inactivated virus.

4) The development of a method for the assay of the protective properties of convalescent serum which has had some use as a prophylactic but of which the value is not yet established.

## *Mumps in M. mulatta*

First of all it was necessary to produce the disease in monkeys. Employing saliva collected within the first 2 days from a typical case of mumps, little difficulty was encountered in producing a marked parotitis following inoculation into Stensen's duct.

* Benjamin Musser Lecture II, The College of Physicians of Philadelphia. Delivered at a joint meeting of the College and the Philadelphia County Medical Society, October 4, 1944.

This condition, even upon cursory inspection, was usually quite apparent. In accordance with the observations of Johnson and Goodpasture the signs of parotitis appeared on the 7th or 8th day after inoculation and consisted in enlargement of the gland itself accompanied by edema of the lower portions of the face. The degree of both glandular swelling and edema varied considerably with the individual animal. In a few monkeys they were minimal and accordingly difficult to recognize. Signs of the experimental disease less regularly seen by us were an increase in body temperature and a leucopenia which Johnson and Goodpasture (1) considered to be constant manifestations.

Reinoculation of the glands of convalescent monkeys with material shown to be infectious for the normal animal did not induce the characteristic symptoms—an indication that immunity had been established. In several animals, however, within 2 or 3 days after reinoculation with active virus a firm hard swelling of the gland was evident on palpation and, in some instances, on inspection. Both the establishment of resistance in convalescent monkeys and the rapid enlargement of the gland in such immune animals were also observed by Johnson and Goodpasture. I wish to call your attention especially to this accelerated swelling since it seems most likely that it is a manifestation of hypersensitivity which develops in the monkey as a result of infection. As I will subsequently indicate, man definitely becomes sensitive to the virus or its products following recovery from mumps.

Although we have carried out most of our work with a single strain of virus, evidence of infection has been obtained with 4 other lots of saliva. The antigenic specificity of these strains, as far as can be determined by means of the complement fixation test, which I am about to describe, was the same as that of the virus originally studied. This suggestion that strains of mumps are antigenically homologous is in accordance with the fact that the immunity induced by an attack is in nearly all cases life-long. If there existed in nature strains of virus which were characterized by qualitatively different antigenic composition, one would expect that second attacks of the disease would be much more frequent. For reasons which will become obvious as we proceed, this conception of the antigenic homogeneity of the virus is of importance.

*The complement fixation test.* Since Johnson and Goodpasture as well as ourselves have demonstrated that a solid immunity develops during convalescence in the monkey, it seemed most probable that, as with many other virus diseases, emergence of antibody in the serum should be one of the marks of such newly acquired resistance. How, then, could this hypothetical antibody be demonstrated? It was an obvious thought to consider the possibility that within the infected gland during some stage of the disease the virus and possibly soluble products derived from it might be present in quantities sufficient to react visibly *in vitro* with such an antibody. Recently the complement fixation reaction has been applied with fruitful results not only in the diagnosis of numerous viral infections, but also in analyses of their epidemiologic behavior. It was, therefore, natural to attempt to learn whether virus material in the infected gland could be used as an antigen in complement fixation tests using convalescent monkey serum as antibody.

To answer this question, the parotid gland of an infected monkey was removed as soon as the signs of the disease were evident. From it was prepared a finely dispersed emulsion in physiological salt solution which was employed as an antigen in the usual manner. It was found that this antigen fixed complement when mixed with convalescent serum, but failed to do so when serum of the normal monkey or one in the earliest stages of mumps was added. Further evidence for the specificity of the reaction was secured by preparing material in the same manner from glands of normal animals and mixing it with convalescent serum. Under these conditions no fixation of complement was noted.

Modifications in the technical procedure of the test have provided us with a satisfactory and sensitive method of determining the presence in tissues and body fluids of small quantities of either antigen or antibody.

*The development and decline of antibody following inoculation.* By means of this test the sera of 59 monkeys before and after inoculation with the virus have been examined. Thus it has been established that no complement fixing antibody can be detected in normal animals but that it uniformly appears within 7 to 14 days after intraparotid inoculation of the virus. As examples the data obtained from 4 animals are presented in table 1.

From the results of experiments in which specimens of sera were obtained at short intervals during several months, it is possible to state that the peak of antibody concentration is reached from about the 12th to 21st day after inoculation. Remaining at this level for about a month or 6 weeks, the concentration thereafter falls rather rapidly to a relatively low titer which usually persists for many months. One animal was found to have antibody in its serum 21 months following recovery. The determination of the antibody-concentration curve has also shown that the factor not only appears very early—even before the symptoms of the disease have entirely subsided—but also abruptly—that is within 24 hours—as shown in table 2.

*Inapparent contact infections in the monkey revealed by the complement fixation test.* A moment ago I said that antibody had not been found in any normal monkey. This is true provided the animal has not been in contact with others which have been recently inoculated with the virus. Earlier in our work when such contact was permitted, antibody was occasionally found in the serum of monkeys which we thought to be normal. Seeking an explanation for such a disturbing observation, a monkey whose serum was shown to be negative was placed in the same cage with an animal freshly inoculated with the virus. Contact was maintained for 5 days when the monkey which had thus been exposed was returned to separate quarters. After about 3 weeks this animal developed complement fixing antibody. Inapparent infection, then, may occur in the monkey on contact with another animal in the incubation period.

All these phenomena are of interest because of their close similarity to the serologic events of the disease in human beings which I will shortly outline.

*The development and properties of the antigen.* The complement fixation reaction has also been used to follow the increase and decline of antigen in the gland. Although we cannot as yet be sure that the antigen is the virus itself, it would seem logical to think that its concentration probably runs more or less parallel to that of virus concentration. On the basis of quantitative determinations of the antigen in 55 glands removed from the 4th to the 8th day after infection, it can be affirmed that the maximal concentration is attained on the 5th or 6th day following inoculation. At this time emulsions from the glands of certain monkeys have been obtained which can be diluted as much as 1:1200 or 1:2000. The average titer of 47 glands, however, was 1:400. Since the mean weight of the gland is about 4 grams, these figures show that sufficient antigen may be obtained for the practical purpose of carrying out the complement fixation test as a routine procedure and for other uses such as the preparation of materials for skin testing and vaccination to which I will subsequently allude.

TABLE I

*Development of complement fixing antibody in monkeys*

| Monkey | CF acute stage | | CF early conval. | | CF after recovery | |
|---|---|---|---|---|---|---|
| | Days after infection | Titer | Days after infection | Titer | Months after infection | Titer |
| 1 | 0 | 0 | 22 | 2170 | 2 | 275 |
| 1937 | 7 | 0 | 18 | 1024 | 3 | 185 |
| 22 | 0 | 0 | 13 | 384 | 3 | <6 |
| 1934 | — | nd | — | nd | 21 | 17 |

TABLE 2

*Development of complement fixing antibody in the monkey. Inoculated 3/30/44*

| Date blood drawn | CF titer |
|---|---|
| 3/23/44 | 0 |
| 3/31/44 | 0 |
| 4/6/44 | 0 |
| 4/7/44 | 96 |
| 4/10/44 | >96 <128 |
| 4/11/44 | 384 |
| 4/19/44 | >384 <1536 |
| 4/28/44 | 1536 |
| 5/12/44 | 384 |
| 5/20/44 | 96 |

With the exception of the parotid gland, the antigen has not been detected in any other tissue or body fluid which we have examined following intraparotid inoculation. These include brain, testis, pancreas, spleen and spinal fluid. Moreover we have not been able to demonstrate its presence in brain or spinal fluid following the introduction of the virus into the cerebral tissue or in the testicle after the inoculation of that organ. If the amount of antigen bears a constant relation to the quantity of virus, it is evident from these

findings that in the monkey very little virus-multiplication, if any, takes place in tissues other than the salivary glands. This apparent refractoriness of the monkey's brain and testis appears to be in contrast to the susceptibility of the corresponding organs in man.

Two of the properties of the antigen are of sufficient importance to deserve brief mention. If the saline emulsion of infected gland at about pH 6.7 be heated at 65°C for 20 minutes, a copious protein coagulum is produced. When this is removed the supernatant fluid is found to contain the antigen in only slightly diminished concentration. The capacity of the virus to cause disease, however, has been destroyed. Again, if an infectious emulsion is treated with 0.3 per cent formol and allowed to stand for 24 hours at 4°C, its infectivity is eliminated but, as we shall see, its capacity to induce the formation of antibody when injected into both monkeys and human beings is retained.

Because of the high cost of the monkey, many attempts have been made to propagate the virus in other species of animals, in the embryonated egg and in tissue culture. So far all have failed. This aspect of the problem, however, is still being investigated.

## The Development of Complement Fixing Antibody Following Mumps in the Human Being

In the light of these experimental results in animals, clearly the next step was to learn whether in human beings an analogous antibody was induced by an attack of mumps. Forty-six typical cases have been studied from which specimens of serum were obtained both during the acute stage and during convalescence. In 33 of the acute sera complement fixing antibody was not demonstrable. On the other hand, it was revealed in all of the sera taken from the same individuals during convalescence. In the remaining sera taken during the acute stage—that is from the 1st to the 6th day of disease—antibody was found. Its concentration, however, was low and in each of these 13 cases the amount of antibody was shown to increase during convalescence. This increase was at least 4 times the initial concentration and frequently much greater. In table 3 a few of the data are presented as illustrations of these phenomena. The initial presence of low concentration of antibody in a minority of these individuals is almost certainly to be accounted for by assuming that the specimen of serum had not been taken sufficiently soon. This assumption is borne out by the fact, which I shall establish immediately, that emergence of antibody frequently occurs within a day or two of the onset.

From each of 11 patients specimens of serum were taken daily for 14 days following the recognition of the disease to learn more precisely when the antibody might be expected to appear and when the highest concentration was reached. Considerable variation was recorded in respect to the time of its appearance. In three instances it was found after 1 day; in 5 after 2 days; in 1 after 5 days and in 2 after 10 days. Maximal titers were recorded in all by the 12th day. Although the numbers are few, it is fairly certain

TABLE 3

*Complement Fixation—Epidemic parotitis*

| Patient | Titer—Acute | Titer—Conval. |
|---|---|---|
| An | 8 | 128 |
| Ed | 64 | 512 |
| Fl | 96 | 384 |
| Ma | 0 | 1536 |
| Mar | 0 | 128 |
| Mo | 32 | 1024 |
| Van | 0 | 384 |
| Wh | 0 | 256 |

that the findings in these 11 cases indicate what one can expect to encounter in the majority of infections. Thus among 33 other patients the data are sufficient to indicate that in only two was the antibody response delayed beyond the end of the 2nd week.

I have discussed these time-relationships in some detail because they are essential in the interpretation of the results of the complement fixation test as applied in the diagnosis of cases where the etiology is not obvious such as orchitis and particularly meningoencephalitis without involvement of the salivary glands. These conditions most often occur as relatively late complications, and so at a time when antibody may have already appeared in considerable amounts.

You will remember that the antibody stimulated by infection of the monkey was found to persist for almost 2 years in the circulating blood. It therefore became of interest to learn whether this phenomenon also might be observed in the human being. Quite evidently if it could be shown that the antibody which developed following an attack

remained for long periods in sufficient concentration as to be demonstrable by means of the test, a method might become available whereby one might distinguish those individuals in a population who at some time in the past had harbored the virus irrespective of whether or not they remembered the event. In other words, the complement fixation test might be employed in the recognition of resistance or susceptibility.

Four adults who had mumps in 1942 and who at that time were shown to develop the antibody as a result of the infection were again tested in 1944. In three instances antibody was demonstrated although, as was to be expected, in amounts much less than those characteristic of the early convalescent phase. It should be stressed that the test on the fourth individual was negative. Further data were afforded by five children who were experimentally exposed to the virus of the 11th monkey passage. All of them developed clinical signs of mumps followed by the appearance of antibody in high titer. Complement fixation tests carried out after about 1½ years showed that in each child the antibody was still present; but again in small amounts. The possible role of intermittent exposure to the disease in maintaining the antibody level could be definitely eliminated in this group of children who were confined within an institution.

These results, then, afford positive evidence that the antibody resulting from an attack of the disease can be demonstrated in most cases for at least 18 to 24 months after recovery. As we shall see, there is reason to believe that it may persist for much longer periods of time. Accordingly it would appear that the test should be useful in discerning the majority of those who have previously been infected.

*The specificity of the antibody.* A word here is necessary in respect to the specificity of the antibody. That it appears regularly and promptly after the onset of mumps and endures for many months following recovery is alone fairly satisfactory evidence for its specific nature. We have, however, examined a number of sera taken during the acute and convalescent phases of several other diseases. In none has the emergence or increase of the mumps antibody been shown. Among these diseases were measles, influenza, lymphocytic choriomeningitis, cervical adenitis, acute sinusitis and nasopharyngitis of unknown origin. This list is not extensive, but it is sufficient to demonstrate the fact that the antibody associated with mumps does not appear *de novo* nor does it increase in amount merely as a result of infection by certain unrelated agents.

### The Complement Fixation Test as a Diagnostic Aid in Meningoencephalitis

Since antibody emerges constantly and in most cases rapidly after the beginning of the disease, it immediately became apparent that the test might be of assistance in the differential diagnosis of aseptic meningoencephalitis.

In addition to that of mumps, a number of viruses and possibly other agents whose nature is quite undefined may give rise to the clinical picture which has been variously designated, but which we shall refer to as "acute aseptic meningoencephalitis." Among the viruses are those of mumps, lymphocytic choriomeningitis, Western equine encephalomyelitis, St. Louis encephalitis, Japanese encephalitis, Russian encephalitis, the virus of louping ill, which is probably identical with that of Russian encephalitis, and poliomyelitis without paralysis. The only means of determining the nature of the virus in any given case is by laboratory procedures which are frequently time-consuming, difficult and expensive. For mumps there has, of course, been no practicable method available.

By means of the complement fixation reaction the sera from 51 patients have been investigated in whom the symptoms and routine laboratory findings were compatible with the diagnosis of acute aseptic meningoencephalitis. With the exception of 17 of these cases in which a varying degree of swelling of one or more of the salivary glands was noted, there were no other distinguishing clinical features. It is therefore unnecessary to present a complete account of the disease as it occurred in these individuals. Allusion should be made, however, to its following characteristics. In all instances in which the spinal fluid was available—and it was obtained from 45 persons—the cell count was elevated. On the average, 90 per cent of the cells in the spinal fluid were lymphocytes. In every specimen the concentration of sugar was normal and no bacteria could be demonstrated by suitable methods of cultivation. A history of exposure to mumps was given by 6 of the 17 individuals with salivary gland involvement and by 10 of the remaining patients.

The results of the complement fixation test in the group of 17 patients with involvement of the salivary glands were as follows. In 10, the ap-

pearance *de novo* of antibody or a significant rise in its titer were recorded. The titers obtained for the other 7 individuals were definitely high, that is they were 1:192 or greater, in the first specimen of serum which was drawn and remained unchanged in subsequent tests.

From what I have already said in respect to uncomplicated mumps, it is clear that when formation or increase of antibody can be revealed, it may be concluded that infection with mumps virus has occurred more or less contemporaneously with the observed symptoms, whatever their nature may be. When these serologic phenomena cannot be demonstrated in cases of meningoencephalitis but a high concentration of antibody is present at the outset, the evidence for recent infection is, we believe, not conclusive but presumptive. This belief is based on the regularity with which high titers are found in individuals just recovering from parotitis compared with the low values almost uniformly exhibited by persons who have experienced the disease at some time in the past. An evaluation of such data has led us to regard a titer of 1:192 or higher as presumptive evidence for a recent experience with the virus.

According to this criterion alone, then, the probability would be great that the illness of these individuals who showed elevated but unchanging titers was due to the virus of mumps. But in this group, of course, the serologic findings were confirmed by patent involvement of the salivary glands. Thus these cases afford a sort of base line or standard by which the results of the tests obtained in the 38 patients who showed no evidence of mumps may be evaluated.

Of these 38 patients, there were 16 who gave either conclusive or presumptive evidence of infection according to the criteria we have just mentioned. It is therefore significant that a history of exposure to mumps was obtained from 10 of them. It is worthy of emphasis that this group represented about one-third of the total number of cases. In contrast the remaining 18 were characterized either by the absence of antibody in their serum both during the acute and convalescent phases or by a low unvarying titer. All the members of this group denied exposure to mumps. In table 4 are presented the serologic findings in a few patients representative of each of the three groups.

In concluding this phase of the subject, it may be instructive to mention the rather extensive list of clinical diagnoses which were made in these groups where the condition of the glands gave no clue to the etiologic agent. The group of 16 showing positive tests included diagnoses of lymphochoriomeningitis, encephalitis, meningoencephalitis, mumps meningoencephalitis and streptococcus sore throat. With the exception of the last, in the negative group these same diagnoses with the addition of poliomyelitis and fever of unknown origin were recorded. Thus the information de-

TABLE 4

*Mumps complement fixation tests in cases of aseptic meningoencephalitis*

| Patient | Serum drawn days after onset | CF titer | Remarks |
|---|---|---|---|
| Wi | 3 | 0 | Mumps 2 days after enceph. |
| | 13 | 384 | |
| Mc | 1 | 384 | Mumps 4 days before enceph. |
| | 8 | 384 | |
| Pl | 3 | 0 | No mumps—Exposed. |
| | 8 | 192 | |
| Sh | 7 | 96 | No mumps—No exposure. |
| | 15 | 384 | |
| Su | 4 | 384 | No mumps—Exposed. |
| | 25 | 384 | |
| Fl | 8 | 0 | No mumps—No exposure. |
| | 47 | 0 | Diagnosis: lymphocytic chorio. |
| Lo | 5 | 24 | No mumps—No exposure. |
| | 20 | 24 | Diagnosis poliomyelitis? |

rived from the application of the test to these 51 cases indicates, I think, that it should assist in the identification of one of the agents frequently responsible for acute aseptic meningoencephalitis.

*The correlation of history of mumps and the results of the complement fixation test. Evidence for the occurrence of inapparent infection.* Let us now review some of the material obtained in carrying out complement fixation tests in normal people. Large groups of Army personnel and of children in institutions have been studied. But since the histories of such individuals in respect to previous attacks of mumps are not reliable and since it is our purpose here to correlate history with the

results of the test in the expectation of being able to make certain deductions, I will present only the data which have been assembled from a study of 344 students at the Harvard Medical School. Every effort was made to get an accurate statement from each of these individuals. From the figures presented in table 5, it is evident that about ⅘ of those who gave positive histories also yielded sera which fixed complement. Thus by means of the test one might expect to be able to recognize about 80 per cent of those who presumably had been infected with the virus. This correlation is approximately what one would predict from the observations which have already been described concerning the persistence of antibody following recovery from attacks which were actually observed, for it will be recalled that in such cases 1 out of 10 persons lost his antibody after about 2 years.

TABLE 5

*Correlation of history of mumps and complement fixation tests: 344 Medical students*

| | History + | | History − | |
|---|---|---|---|---|
| | CF + | CF − | CF + | CF − |
| Per cent | 45.9 | 12.3 | 18 | 23.8 |
| Correlation with history | .79 | | .57 | |

In contrast to the fairly high correlation between a positive history and a positive test, that between a negative history and a negative test is little better than 50 per cent. Now in view of all the evidence presented so far, a positive test may be taken to signify a previous infection. Since nearly one-half of those who denied ever having had mumps yielded positive sera, it would therefore seem necessary to infer that these persons had experienced an inapparent infection by the virus as a result of which antibody was produced and immunity presumably established.

This indication of the existence of inapparent or silent infections is in keeping with the epidemiologic fact that although the disease is common and thus opportunity for contact with the virus is frequent, only from 50 to 60 per cent of adults admit that they have had mumps. Should, however, the percentage of inapparent infections revealed by our survey be shown to hold true for the adult population in general, then the total of those in whom an infection of some sort has occurred would be at least 70 to 80 per cent. This incidence begins to approach that of measles in which there is little evidence of inapparent infection. It is also more nearly of the magnitude one would expect in the case of a disease which is so widespread.

No systematic attempt has been made to correlate the persistence of antibody with the interval elapsing between the attack of mumps and the testing of the serum. This interval has varied from 1 to more than 15 years. It is our impression, however, gained not only from findings in this group of medical students, but also from the results obtained in a limited number of older individuals, that the lapse of time is not so much the determining factor in the persistence of antibody as variation in the individual himself. That is to say, certain persons tend to lose the capacity to maintain the antibody much sooner than others.

Of course it is impossible to be sure that this immunologic habitus, as it were, is the only factor concerned, since one cannot exclude the possibility that repeated exposure to the virus has occurred in some cases. Such exposure would obviously serve to maintain an appreciable antibody level in the blood whereas in others who have escaped intermittent contact with the virus, the lack of antigenic stimulation would permit the antibody to fall below the detectable threshold.

*Correlation of the results of the complement fixation test with resistance and susceptibility.* Everything that had been done up to this point strongly supported the hypothesis that persons who were complement-fixation-positive, whether or not they acknowledged an overt attack, should prove resistant on exposure to the virus. Conversely, a considerable proportion of those with negative tests should on such exposure develop the disease. But direct evidence for this interpretation of the results of the test were lacking.

A situation very fortunate from our point of view arose in an institution for children here in Philadelphia. In one of the large dormitories of this institution a case of mumps appeared on January 12, 1943. Most of the children residing in the dormitory apparently were exposed to the primary case. A quarantine of this unit was immediately established which seemed to be effective in preventing the disease from spreading to the inmates of two other houses. Soon after the primary case was recognized, specimens of serum were obtained from 148 of the children living in the same building and complement fixation tests

were carried out. The results are recorded in table 6.

It will be seen that during the month of February a total of 32 cases of mumps occurred in the dormitory. With a single exception all of these appeared among the 70 children whose tests were negative. The specimen of serum obtained from the lone individual who developed the disease in the positive group fixed complement to a minimal degree only. With a difference of this magnitude in the incidence of the disease in the two groups, it is scarcely necessary to apply statistical techniques to demonstrate significance. However, when this is done it is found that the probability of the observed distribution occurring by chance is extremely small.

TABLE 6

*Correlation of results of complement fixation tests and susceptibility to mumps. Epidemic at Pennsylvania School for the Deaf Cresheim Dormitory*

| | |
|---|---|
| No. individuals tested | 148 |
| Positive tests | 61 |
| Negative tests | 70 |
| Doubtful tests | 4 |
| Unsatisfactory tests | 13 |
| Total cases of mumps | 32 |
| No. in positives | 1 |
| No. in negatives | 31 |

Additional direct evidence of the same sort was derived from the experiment involving the artificial exposure to the virus which I mentioned previously. As controls 5 individuals with negative and 3 with positive tests were inoculated into one parotid duct with monkey passage virus. All those with negative tests developed typical mumps with extension to other glands. In contrast, those with initially positive tests failed to exhibit the characteristic signs of the disease, although like the immune monkey, early swelling of the inoculated gland was observed. Since these subjects were given doses of virus which were without doubt much larger than would ever be received in the natural manner, the results are to be regarded as most significant.

This closed epidemic at the Pennsylvania School for the Deaf likewise served to furnish cogent evidence for the occurrence of inapparent infections. Thus about one month after the outbreak had come to an end, 59 of the 70 children who originally gave negative tests were bled and their sera re-examined. In accordance with expectation, all of the 31 individuals in whom the disease was recognized were strongly positive. Sixteen others who never had mumps, however, likewise exhibited a reversal of their tests from negative to strongly positive and 2 more gave definite though weaker reactions. Only 9 of these children, therefore, failed to show changes as a result of the passage of the epidemic through their midst. The results of such repeated tests on negative sera from 29 inmates of the 2 other dormitories where outbreaks did not occur showed that no change had taken place during the time the epidemic was in progress. Plainly where opportunity for exposure was lacking, the immunologic status remained the same.

We have discussed this serologic evidence for inapparent infection in a rather detailed manner, not only because of its practical bearing upon the problem of the control of mumps epidemics, but also because it would seem to afford a good example of certain fundamental immunologic and epidemiologic principles.

## Dermal Hypersensitivity Induced by Infection with the Virus of Mumps

We turn now to a discussion of another possible means of determining whether or not infection has occurred. Since the classical studies of von Pirquet (4) on the nature of the accelerated and immune reactions in persons partly or wholly resistant to vaccinia, it has been known that a hypersensitive state may be induced as a result of infection by a virus. Surprisingly little attention, however, has been paid to viral hypersensitivity with the single exception of its use as a practical diagnostic measure in the form of the Frei test. Perhaps a renewal of interest may now occur since very recently Beveridge and Burnet (5) have reported that in certain persons a local allergic reaction follows the intradermal inoculation of inactivated influenza virus—an observation which has been made independently in our own laboratory by Dr. Lewis W. Kane.

With these thoughts in mind, it seemed possible that mumps virus also might establish as an additional sign of its passage an allergic condition which could be brought to light by injecting inactivated virus in the form of a heated suspension of the infected parotid gland. Moreover, the accelerated swelling of the gland in the reinoculated immune

monkey to which we have already referred suggested the existence of hypersensitivity attendant upon infection.

Acting upon these ideas, 0.1 cc of heated and diluted virus suspension was injected intradermally into a few individuals some of whom gave positive and some negative histories of mumps. As a control for the specificity of any reaction which might ensue, an equivalent quantity of a suspension prepared in the same manner from the gland of a normal monkey was also injected. The individuals with positive histories all responded by showing after 24 to 48 hours a zone of erythema about the site of inoculation with slight induration near the center which varied from about 1 to 5 cms in diameter. At the site of the control injection no reactions were noted. In contrast most of those who gave negative histories did not react to either the virus material or the normal tissue suspension. This preliminary experiment seemed, then, to support the hypothesis that infection with the virus led to the establishment of an allergic state which could be demonstrated by inoculation of this heated material.

Studies were then undertaken to explore the significance of this phenomenon which in principle were entirely analogous to those employed for the same purpose in the case of the complement fixation test.

*The development of hypersensitivity following observed attacks of mumps.* Skin tests have been done in 6 individuals who exhibited typical parotitis. The tests were carried out either before the inception of the disease or during its acute phase and again in convalescence. In most instances no reaction was seen until after recovery had occurred. At this time, of course, complement fixing antibody had already developed. The skin test has also been observed to change from negative to positive as the result of inapparent infection. This occurred in a laboratory worker who developed antibody several months after she had begun to handle the virus of mumps. No symptoms were noted, however, at any time. This was construed as evidence for inapparent infection. A skin test done before antibody appeared was negative but became positive after the emergence of the antibody.

Accordingly, we may tentatively conclude on the basis of data obtained from the study of these 7 cases that like so many other infectious agents the virus of mumps gives rise to a hypersensitivity of the tuberculin type. It is important to make it perfectly clear that this hypersensitivity is associated with an infection which can be either overt or unrecognized.

The available evidence indicates that there is no direct relationship between this hypersensitivity and the complement fixing antibody. Thus parallel determination of antibody and skin reactivity in 4 of the 6 cases of mumps which we have just mentioned showed that in all of them antibody developed before the allergy became manifest. In two instances several weeks intervened between their respective appearances. This fact carries a very definite practical implication. Although in a few individuals the skin test has been observed to be positive early in the disease, in the majority the allergic state is not established until after recovery. Accordingly it is not expected that the test will prove of much assistance for the rapid diagnosis of infection with the virus. From the standpoint of retrospective diagnosis, however, the test might be of assistance, provided a negative result had been obtained at the time the disease was active.

*Correlation of the result of skin test in normal individuals with the history of mumps.* The skin test, on the other hand, if it could be shown to distinguish with a reasonable degree of accuracy between the susceptible and insusceptible members of a population might be very useful since it is much more conveniently carried out and requires the preparation of relatively little material as contrasted with the complement fixation reaction.

To learn, therefore, whether or not it might be a suitable instrument for this purpose several hundred tests have been done. No systemic or severe local reactions have occurred in any instance. A very small percentage of those tested have reacted to the control material; but among entirely normal personnel this number is so small as to be negligible. But among tuberculous children and the feeble-minded and idiotic nonspecific reactions were encountered not infrequently and did somewhat impair the results of the surveys in these groups.

On account of the reliability of the data, in correlating the history with the results of the skin test we will again confine ourselves to the tests done on 97 students and other personnel at the Harvard Medical School. The results are summarized in table 7. Here we find that everyone who recollected having had mumps reacted to the virus. The correlation with history is definitely higher than that of the complement

fixation test. This suggests that allergy to the virus can be demonstrated in certain individuals in whom the antibody has sunk to a sub-threshold level, and accordingly that the skin test in most instances should prove to be an even more accurate index of past infection than the determination of antibody. On the other hand, when we examine the reactions in those giving a negative history, about the same distribution is noted as occurred with the complement fixation test.

TABLE 7

*Correlation of history of mumps and results of skin test Medical students and personnel at H. M. S.*

| | History + | | History − | |
|---|---|---|---|---|
| | ST + | ST − | ST + | ST − |
| Medical students | 35 | 0 | 17 | 19 |
| Personnel | 14 | 0 | 4 | 8 |
| Total | 49 | 0 | 21 | 27 |

TABLE 8

*Correlation of results of skin and complement fixation tests: Medical students and personnel at H. M. S.*

| | Comp. Fix. + | | Comp. Fix. − | |
|---|---|---|---|---|
| | ST + | ST − | ST + | ST − |
| Medical students | 42 | 0 | 6 | 27 |
| Personnel | 13 | 1 | 6 | 7 |
| Total | 55 | 1 | 12 | 34 |

Almost one-half of those who denied mumps exhibited positive skin reactions. The test for allergy, then, appears also to be capable of uncovering those inapparent infections of the past.

Complement fixation tests were done on the same individuals just before the skin tests were carried out. The data obtained by these two procedures are presented in table 8. Evidently there is a very close agreement between the results when the complement fixation test is positive. It will be seen that in only 1 case was antibody present when the skin failed to react. The correlation is lower, however, when antibody was absent. Thus about one-quarter of those giving negative fixation were skin-positive. This may be taken as further evidence that the skin test in the majority of cases is the more delicate index of past infection. Nevertheless we may expect to encounter on rare occasions positive fixation in an individual who fails to give the derma response.

## Correlation of the Results of the Skin Test with Resistance and Susceptibility

On the basis of the facts concerning the skin test which I have presented, it would be expected that only negative reactors upon exposure should develop the disease. This expectation has been largely confirmed by the outcome in two epidemics. The first of these took place in a boys' boarding school and the second in a unit of a children's institution. Within a few days after the primary case appeared at the boys' school, skin tests were done on contacts who gave negative histories. The pertinent data derived from this experience

TABLE 9

*Correlation of results of skin tests and susceptibility to mumps*

| St. Paul's School epidemic | | | |
|---|---|---|---|
| Boys tested | 62 | Total cases mumps | 19 |
| No. positive | 14 | Cases in positives | 1 |
| No. negative | 41 | Cases in negatives | 17 |
| No. doubtful (< 10 × 10 mm) | 7 | Cases in doubtfuls | 1 |

are given in table 9. It will be seen that 17 of the total 19 cases which developed occurred in the group of 41 negative reactors. The disease was apparent in only one individual of the 14 in whom we considered the test to be definitely positive. Another individual developed mumps whose test was considered doubtful, that is less than 1 cm in diameter. Although the number of negative reactors was much larger than that of the positives, the difference in the percentage of those who came down with the disease in the two groups is statistically significant.

In the children's institution skin tests were carried out on the majority of the inmates of the building in which the primary case was observed. The results are summarized in table 10. Here 7 cases developed, and 6 of them were in those whose tests had been shown to be negative. The 7th occurred in a boy who reacted both to the virus and the normal parotid suspension and therefore his test was recorded as doubtful. Again, the percentage difference is significant even if this individual be considered as a positive reactor.

A study of an epidemic among the students at the Atlanta Dental College by Lieutenant Gellis, attached to the Army Commission on Measles and Mumps, yielded similar results. There, however, the percentage of those who came down with the disease was somewhat higher among the group of positive reactors.

From the data so far available, I believe it is reasonable to conclude that by means of the skin test one may detect a large proportion of those who will develop the disease if the exposure is adequate. But it must be frankly admitted that a few susceptible individuals will be missed. Further work is in progress to learn more concerning the optimal quantity of material to be employed and the degree of reaction which can be taken as indicative of resistance. In this way we hope to increase the accuracy of the procedure.

TABLE 10

*Correlation of results of skin tests and susceptibility to mumps*

| Skillman Village epidemic | | | |
|---|---|---|---|
| Boys tested | 92 | Total cases mumps | 7 |
| No. positive | 40 | Cases in positives | 0 |
| No. negative | 38 | Cases in negatives | 6 |
| No. doubtful (< 10 × 10 mm) | 14 | Cases in doubtfuls | 1 |

## Experiments on Active Immunization with Formolized Virus

*Experiments in monkeys.* I will now, as briefly as possible, summarize the experimental work which has been done with the purpose of finding a method of prophylactic vaccination.

Not very long ago nearly all investigators in the field believed that an effective immunity could only be produced following the inoculation of material containing active virus, although this might be in a relatively attenuated state. It is now evident that this conception was erroneous and that it is possible to immunize effectively with certain viruses which have been rendered incapable of causing disease. Formol, as an inactivating agent in the preparation of such vaccines, has been extensively employed.

The demonstration of large amounts of antigen in the infected monkey parotid suggested that emulsions of this organ might provide an effective vaccine after the activity of the virus had been eliminated by formolization. Accordingly such vaccine was prepared and injected subcutaneously into monkeys. Usually 2 doses of 0.5 cc each containing a 2.5 or 10 per cent suspension of the gland were administered at an interval of 5 days. From 10 to 14 days later the monkey was inoculated by the intraparotid route with active virus. As an index of the protective effect of the vaccination the antigen content of the glands was determined and compared with that of the glands from one or more unvaccinated control monkeys which had received the same challenge dose of active virus.

The results of 7 experiments of this sort are summarized in table 11. Taken as a whole the majority of monkeys which were vaccinated yielded glands that contained definitely less antigen than those of the controls. In the glands from

TABLE 11

*Complement fixing antigen in glands of normal and vaccinated monkeys after inoculation with virus of mumps*

| Glands from | Glands having titer of | | | |
|---|---|---|---|---|
| | < 150 | | > 150 | |
| | No. | Per cent | No. | Per cent |
| Normal monkeys | 5 | 10 | 44 | 90 |
| Vaccinated monkeys | 16 | 59 | 11 | 41 |

5 of the 18 animals which received vaccine no antigen at all could be detected. Since it has also been shown that after recovery from experimental mumps, antigen cannot be revealed in the gland following challenge inoculation of active virus, we may assert with considerable confidence that the injection of formolized vaccine leads in many instances to a definitely determinable increase in resistance. It is evident, however, that such resistance is often not absolute and occasionally fails to appear at all.

That the vaccine was also capable of inducing the formation of antibody was shown by the fact that of 18 monkeys, 13 showed positive complement fixation tests as a result of the vaccination.

*Experiments in human beings.* Because of these suggestive findings in animals and because of the great advantages an effective vaccine would offer in the control of epidemics in the armed forces and elsewhere, it was considered justifiable to undertake experiments in human beings.

Arrangements were therefore made by Dr. Joseph Stokes, Jr. and Dr. Elizabeth P. Maris of the Children's Hospital, Philadelphia, to carry out such investigations in two institutions where presumably susceptible groups of children were selected by means of the complement fixation test. In the first experiment 7 of 13 individuals were given two doses of the formolized vaccine at an interval of 7 days. Sixteen days after the last dose of vaccine, active virus was inoculated via Stensen's duct into the right parotid gland. At the same time the remaining five subjects received the same dose of virus. Complement fixation tests done at the time of the challenge inoculation showed that 4 of the 7 vaccinated children had developed antibody as a result of the vaccination. No antibody was demonstrated in any of the controls. After a period of about seven days the signs of mumps were observed in all the controls. In contrast only 2 of the vaccinated experienced a typical attack of the disease. Nevertheless some degree of swelling of the inoculated gland was observed in all of the vaccinated group. In five the swelling, however, occurred earlier than it did in the controls and in the 2 vaccinated children who developed typical mumps. This accelerated reaction was entirely analogous to that which occurs in the immune monkey when active virus is injected. In the control group involvement of the other parotid or the submaxillary glands was a constant feature, whereas in the 5 vaccinated individuals who failed to develop typical mumps, extension to these other salivary glands did not occur.

The second experiment was essentially a repetition of the first except 3 children whose complement fixation tests were found to be positive were included as so-called positive controls in order to determine directly whether the presence of antibody could be taken as an index of resistance. They were not vaccinated. Nine individuals with negative complement fixation tests received the vaccine and an equal number of negative reactors were reserved as controls. Of the 9 vaccinated children, 5 developed antibody as the result of injections of inactivated virus. With the exception of two of the vaccinated subjects who were inoculated by simply spraying a suspension of virus into the oral cavity, all the others were given the challenge dose via the right parotid duct.

The results were similar to those of the first experiment. All the controls, with one possible exception, whose complement fixation tests were negative developed typical mumps with extension to the uninoculated glands. Six of the vaccinated group ran an atypical course characterized by early swelling of the inoculated gland but by little or no involvement of the others. This same picture was observed in the so-called unvaccinated positive controls. The incubation period was

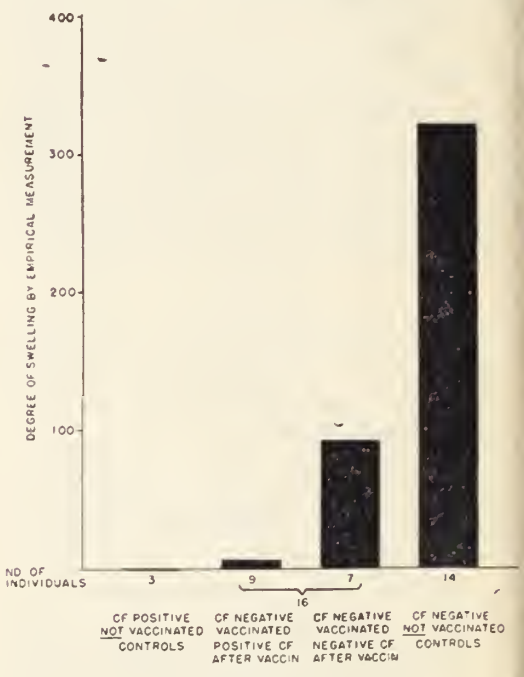


CHART 1

ACTIVE IMMUNIZATION AGAINST MUMPS

Degree of swelling, exclusive of gland injected, after challenge exposure to active virus injected into one parotid duct 14–17 days after vaccination.

again about 7 days except in the case of one of the boys who received the active virus as a spray. Here the symptoms did not appear until about the 14th day after inoculation.

To illustrate graphically the differences between the vaccinated and non-vaccinated in both experiments, the degree of swelling noted in the glands which were not inoculated is represented in chart 1. The degree of swelling of the inoculated gland has been omitted since it is impossible to be entirely certain whether the early enlargement of this organ which occurred in many of the vaccinated represented the result of a true infection by the virus or an allergic response to its presence.

From the chart it will be observed that in gen-

eral those individuals who responded to the vaccine by the formation of complement fixing antibody showed the least evidence of involvement of the uninoculated glands. There was an occasional exception to this rule, however, and it would be unsound to conclude that this antibody was directly involved in protection against the virus.

The short incubation period following intraparotid inoculation is worthy of brief comment. It is precisely that characteristic of the experimental disease in the monkey and of course much shorter than that of the disease acquired in the natural manner. In contrast, the boy who received sprayed virus had a period of incubation approaching that of the natural disease. These facts suggest that in the pathogenesis of mumps the virus may enter the parotid gland by a route other than directly via Stensen's duct.

TABLE 12

*Inhibitory effect of human convalescent mumps serum on the development of complement fixing antigen*

| Monk No. | Inoculum | Titer of antigen in parotid gland |
|---|---|---|
| 18 | Virus 1:80 and serum | 52 |
| 19 | " 1:40 " " | 150 |
| 20 | " 1:20 " " | 75 |
| 21 | " 1:40. No serum | 1200 |
| 22 | " 1:160. " " | 600 |

In estimating the significance of these attempts to vaccinate against mumps, it is perhaps fair to regard the results as suggestive and encouraging. Although in some instances there is indication that the vaccine increased the resistance, it is only too clear that in others it completely failed to do so. At the moment another experiment is in progress in which the challenge inoculation of virus has been administered as an oral spray to eliminate the confusing presence of the early swelling of the inoculated gland.

*Experiments in monkeys on the virus-neutralizing properties of convalescent serum.* There have been numerous reports in the literature on the use of convalescent mumps serum as a prophylactic. We therefore attempted to determine whether or not the multiplication of virus as estimated by the quantity of antigen formed in the gland could be checked or prevented when convalescent serum was added to the virus and the mixture injected into the monkey. The combined results of 2 experiments of this kind are presented in table 12. It is evident that under these conditions which should favor any anti-viral property of the serum, complete suppression of the formation of antigen was not obtained. It will be observed, however, that the serum did exert some inhibitory effect since the quantity of antigen in the glands of the animals which received the mixtures of virus and serum was much less than in those of the control monkeys which were given only virus.

It should be pointed out in respect to further investigations of the problem of passive immunization in mumps that although the complement fixing antibody cannot be identified with a neutralizing factor, the technique of measuring its concentration offers a means of comparing the antibody content of various lots of convalescent serum. The complement fixation test has been employed in this manner in the assay of various lots of a human globulin concentrate which has proved of definite value in the prophylaxis and modification of measles (6).

## *Summary*

In place of the traditional recapitulation, we may perhaps see how far we have come toward the attainment of the objectives which were outlined at the beginning.

It would seem as if in the complement fixation test a laboratory method of diagnosis had been made available which should be of particular assistance in situations where infection by the virus of mumps is suspected but where decision cannot be made solely on the basis of the clinical signs. Acute aseptic meningoencephalitis without involvement of the salivary glands is the most important of these conditions.

Both the complement fixation test and the skin test for dermal hypersensitivity, although their accuracy, like all such procedures based on immunologic phenomena, is not absolute, afford means of revealing the majority of individuals in a population which are on the one hand immune or on the other potentially susceptible. Since the skin test is by far the simplest procedure, it is probably the method of choice for this purpose, especially if further studies lead to a better understanding of its limitations.

As yet satisfactory ways of inducing either active or passive immunity have not been devised. The experimental data on the effect of prophylactic vaccination with formolized suspensions of monkey virus do, however, hold out the hope that the

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problem of active immunization can be solved. Although I am inclined to believe that passive immunization in mumps will not prove to be effective, a method is now available which, if desired, could provide a provisional standard for the assay of various lots of convalescent sera.

In addition to the possible application of some of these observations to practical ends, I wish in closing to suggest that their principal value might lie in their contribution, however small, to our general understanding of the epidemiologic behavior of infectious diseases and of the factors concerned in that enduring type of immunity which some of these diseases confer on the individual.*

* In the experimental work outlined in this lecture, the colleagues of the author were Doctors Sidney Cohen and Lewis W. Kane, of the Harvard Medical School, and Doctors Joseph Stokes, Jr. and Elizabeth P. Maris, of the Children's Hospital, Philadelphia, and the University of Pennsylvania, the School of Medicine. For their essential cooperation in supplying clinical material, we are greatly indebted to Doctors Conrad Wesselhoeft, Charles A. Janeway and Edwin H. Place of Boston; Dr. Francis G. Blake, of New Haven, and Major Aims C. McGuinness, A.U.S.

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# The American Medical Argonauts
# Pupils of Pierre Charles Alexandre Louis

*By* GUY HINSDALE, M.D.

*Charlottesville, Va.*

*Fellow, and Former Curator of the Mütter Museum, of the College of Physicians of Philadelphia*

*Therefore, my lords, omit no happy hour*
*Which may give furth'rance to our expedition*
*For we have now no thought in us but France.*
*Shakespeare, King Henry V, Act I, Sc. 2.*

THE great discoveries by French scientists and the contributions made by Frenchmen to medical and surgical knowledge are known the world over. There was a period a little over a hundred years ago when American physicians were especially attracted to the medical and surgical clinics of Paris. It was more than an interlude; it was an era, a period between the popularity of Edinburgh and London clinics, and those of Vienna and Berlin.

The British schools were by no means declining but there were some exceptionally brilliant teachers in Paris who were destined to influence medical thought for generations. Laennec, Piorry, Andral, Trousseau, Chomel, Louis and Broussais were among the medical teachers and Dupuytren and Philibert Joseph Roux among the surgeons.

In the decade 1830–1840 American students of clinical medicine invariably sought Louis, a physician in turn to three hospitals, and he accepted many of them as private students and cordially invited them to join *La Société d'Observation Médicale* of which he became the perpetual president.

Before this some Americans of the Revolutionary period had made the journey to Edinburgh and London but, owing to wars raging on the continent the incentive to foreign study was lost a while. But by 1830 when Louis Philippe ascended the throne international relations were much better although in Paris itself there was great political unrest fomented by the display of wealth by the rich and the poverty of the lower classes. It was a dark and stormy period with much criticism of the king.

Louis must have been a most engaging person. As Osler says: "In Louis, even more than in Laennec, the young American students of that day found light and leading." He was born in the village of Ai, Champagne, and after receiving his medical degree in Paris he was urged by a friend to make a journey to Russia where he became licenced to practice and remained six years but in 1823 he returned to Paris to work as a clinical clerk at La Charité by invitation of Chomel. From his thirty-third to his fortieth year he then devoted his time to the most rigorous and impartial medical observation and a meticulous numerical analysis of clinical symptoms.

The hours observed by students were from 6:30 A.M. until bedtime. Visits were made at all the hospitals by candle light and a lecture was delivered at most of them immediately after the visit. It was through this training that Louis was able to fire his pupils with ambition to learn the truth no matter how laborious his methods were. As one of his American pupils, Oliver Wendell Holmes, said: "I learned three things in Paris:—not to take authority when I can have facts; not to guess when I can know; and not to think a man must take physic because he is sick."

Louis's pupils acquired a timely distrust of drugs and through personal contact with him a refinement and culture characteristic of the French gentleman. Another pupil of Louis, the late Prof. Alfred Stillé, in a letter to Osler said that Louis's methods were laborious and that they gratified too little the thirst for popular applause and personal exaltation that contaminates so many, even men of merit. Louis stated his belief that

"the truth is in the facts and not in the mind which observes them."

An opportunity came to Louis in 1828 to join Mm. Chervin and Trousseau as members of the Commission of the French Government to study an epidemic of yellow fever which raged from August to December in Gibraltar. They arrived thirty-three days before the end of the epidemic and were given all the privileges that the military officers and the surgeons of the English forces could afford. The epidemic subsided only after the occurrence of a violent hurricane.

In making their report, however, the commission were not agreed as Chervin did not believe in the contagiousness of the malady. As a result of this study Louis wrote a book on yellow fever and he intrusted the manuscript to a favorite pupil, Dr. George C. Shattuck, of Boston, who translated it and that was how Louis's work on yellow fever first appeared in English in Boston.

It is interesting to note the method of treatment used at that time. One patient was given one and a half ounces of castor oil, an oil enema and leeches to the temples. Later he was given three grains of calomel every three hours and eighteen leeches were ordered to the temples. He was also bled sixteen ounces. He was then given an effervescent draught and four grains of calomel with laudanum. On the fourth day he died.

Louis also later disagreed with Broussais whose opinions on the nature of phthisis he did not share; nor did he agree with him on "l'action typhoide." Broussais's star declined while Louis's continued in the ascendant.

Another interesting sidelight on the medical practice of the day is given in Louis's treatise on phthisis. It occupied him for five years and appeared in 1825. As would be expected, it is most methodical and at the end there is a chapter on treatment and various remedies popular at that time were mentioned only to meet disapproval. They are now forgotten. Sea salt was one. Louis used it for five months in 1839 in the case of every patient with phthisis in the wards of Hôtel Dieu. Most of them took it for a month or upward, but no improvement was observed. He also tried "protoioduret of iron" but found no improvement. Sesquioxide and lactate of iron met with the same result. Subcarbonate of potassium was tried but no benefit was observed; likewise with chloride of lime. He tried out chlorine gas in fifty cases at La Pitié, Hôtel Dieu and l'Hôpital Beaujon with no success. Digitalis was also found unsatisfactory. Creosote and iodine (Magendie's formula) were also disappointing. Louis used sedatives like opium, stramonium, belladonna and hyoscyamus for cough and he denounced lavish bleeding commonly practiced at the time. Catechu, a tonic to the mucous membrane, was approved with diascordium.

This work "Researches on Phthisis" was translated for the Sydenham Society by Dr. Hugh Hale Walshe of University College, London, the second edition appearing in 1846. In it the author describes himself as Physician to the Hôtel Dieu; Perpetual President of the Medical Society of Observation; Member of the Royal Academy of Medicine; Honorary Member of the Medical Societies of Massachusetts and of Edinburgh; of the Provincial Medical and Surgical Association of England; Fellow of the College of Physicians of Philadelphia; of the Royal Academy of St. Petersburg; of the Medical Societies of Heidelberg and Bruges; of the Medical Society of Observation of Boston. It was dedicated to Chomel.

In turn Louis's pupils and colleagues dedicated their best works to him. They included Bazin, of Bordeaux; Grisole of Paris; Carl Hecker, of Berlin; Marshall Hall, of London; Leuret, of Bicêtre, Paris; Valleix, of Toulouse and Paris, and Woillez, of the lunatic asylum of Clermont.

In planning his "Researches on Phthisis" Louis grouped the cases he observed in Chomel's wards at La Charité from October, 1821, and analyzed them very carefully, spending three, four and sometimes five hours daily at the hospital and at least two hours at each *post mortem* examination. He counted the number of instances in which certain symptoms or anatomical changes have occurred in order to determine their true value. It was the method of numerical analysis and followed closely Morgagni's dictum:—There is no better way of arriving at the truth than to observe as many cases as possible and then draw conclusions (*De Sedibus et Causis Morborum*).

After spending two years or more in collecting and analyzing his notes he discarded the earlier cases because he had omitted to note the condition of the intellectual faculties of his patients; and he was very careful not to ask leading questions, but elicit, as far as possible, spontaneous answers.

It was Louis's second great work that appeared in 1829 that drew to him the majority of American students, especially during the decade that was to

follow. It was entitled "Anatomical, Pathological and Therapeutical Researches on Gastroenteritis, Putrid, Adynamic, Ataxic Typhoid Fever." Its influence will be seen shortly. Louis published five volumes on internal medicine and his fame spread.

Word came to America of the growing brilliance of the French clinicians and very likely it was Elisha Bartlett, of Rhode Island, a graduate of Brown University, who inspired the New England group to go abroad as he had done after receiving his degree in 1826. He went first to Paris and then made a trip to Italy with Dr. Southwick, of Boston. Bartlett spent May in London and he sailed from Liverpool on his return trip June 8, 1827.

The Americans who visited Paris for medical study in the ensuing decade did not go as a group like the argonauts of old with Jason in the Argo in search of the Golden Fleece, but they were actuated by the same high motive and were individually attracted by the fame of certain teachers of medicine or surgery. Between 1830 and 1850 the medical clinics of Paris were at the greatest height of their popularity.

Before steamships and in comparatively small vessels the hardships of the voyage had to be met with courage and determination. Their watchword must have been "Let nothing you dismay." It was the day of rugged individualism. They went early in life and stayed long, some as much as two or three years. Oliver Wendell Holmes was one of these Argonauts and, perhaps, the most famous. He sailed from New York in 1834 on the packet ship "Philadelphia," landing in Portsmouth after a voyage of twenty-four days. After a week in the south of England visiting the Isle of Wight, Stonehenge and Salisbury, he crossed the Channel to Havre, going from there to Paris. Besides the time spent in the Paris clinics Holmes made a wonderful tour of England, Scotland and, later, Switzerland and Italy.

It was in Louis's clinics that Holmes spent most of his time while in Paris and he laid a broad foundation for his subsequent career as professor of anatomy, for a time also holding the chair of physiology at Harvard Medical School; but he later confined his teaching to anatomy alone. In Paris Holmes met other Americans whom we shall refer to. At the end of his long visit Holmes sailed on the packet ship "Utica" reaching New York in forty-two days.

William W. Gerhard was one of the earliest American pupils of Louis. He was born in 1807 and was graduated from the University of Pennsylvania in 1830 and he led off the Philadelphia delegation of the argonauts. He went to Paris in 1830, becoming a student of Louis and, with Norris, Pennock, James Jackson, Jr., and Holmes he formed a private class for which they gave Louis a handsome recompense which was most highly appreciated. With Pennock he described Asiatic cholera in 1832.

Gerhard was deeply impressed with Louis's teaching and made the important deduction that the so-called typhus fever was in reality to be more properly classified as two separate diseases, one of which is to be called typhoid. His two papers published in the *American Journal of the Medical Sciences* in 1837 definitely settled the clinico-pathological status of the two diseases. Osler said that this paper was the first in any language to give a full and satisfactory account of the clinical and anatomical distinctions we now recognize.

In 1833 Gerhard returned to the United States and was elected a resident physician in the Pennsylvania Hospital and while there he demonstrated that the "common continued fever" in Philadelphia was identical with the typhoid of Paris. In 1836 he studied hundreds of cases of typhus and showed its dissimilarity to typhoid of which he observed 214 cases in the Pennsylvania Hospital. His European training soon put him in the first rank. It should be remembered that at this time Gerhard was only thirty years old; but at twenty-eight he had become assistant professor of the Institutes of Medicine in the University of Pennsylvania.

Gerhard soon became recognized as one of the foremost pathologists in the United States. With Norris, Stillé, Goddard, Pennock, Pepper, Mütter, Carson and others he joined in forming a pathological society in 1838. He was, very naturally, made president and is now the patron saint of the Philadelphia Pathological Society. This society founded in 1857 in the Pennsylvania Hospital is an offshoot of the earlier society and is one of the oldest in the world.

In 1837 Dr. Gerhard contracted typhoid fever but this did not prevent him from making another trip to Europe in 1843.

Among the first Philadelphians to attend the lectures of Louis and other clinicians was George W. Norris. He sailed in 1833 making the voyage

in thirty days, and in Paris met his fellow students; Dr. William Pepper, *primus*, Dr. Gerhard, Dr. Holmes and others. Norris was invited to join La Société Médicale d'Observation of which Louis was president. Norris was then twenty-five and in Paris he developed an interest in surgery and besides those of Louis, he attended the surgical clinics of Dupuytren, Velpeau and Roux. On returning to America he continued his surgical work and at forty was made professor of Clinical Surgery in the University of Pennsylvania, a position he held until 1857. He died in 1875 after devoting his life to writing and teaching.

Other Philadelphians in Paris at that time were Thomas Stewardson and Caspar Wistar Pennock.

I am indebted to Dr. George Cheever Shattuck, of Boston, for information about his grandfather, George Cheyne Shattuck, the younger, who was one of Louis's pupils having spent nearly three years in study abroad. After receiving his medical degree from Harvard in 1835 he sailed for Europe the next year. On reaching Paris he spent his time in the French hospitals, taking private courses in auscultation, chemistry and pathology and he devoted much time to Louis's clinics. Here he met Dr. Alfred Stillé, of Philadelphia. They were very congenial and spent a vacation together in Italy and were joined by Dr. Alonzo Clark who then hailed from Vermont. Munich and Vienna came next in their itinerary.

Dr. Shattuck later made the acquaintance of the leading physicians of London, Edinburgh and Dublin. Louis made a lasting impression on him because of his analytical method of investigation of cases and for important advances in the pathology of tuberculosis, or phthisis as it was called then. This was the time that Louis made his great study of typhoid then prevalent in Paris and he associated it with lesions of Peyer's patches, perforations of the intestine and splenic enlargement. He distinguished typhoid from other forms of enteritis but he had not yet studied typhus in the same way. Louis suggested that Shattuck investigate the continued fevers common in England. This resulted in Shattuck's most valuable contribution to medical literature. In this study he observed thirteen cases during life and made several autopsies. By dividing into groups and contrasting them he pointed out differences in the character of the eruption, the abdominal symptoms and the age and incidence. One of the cases showed lesions of Peyer's patches and today would have been recognized as typhus. Typhus is common in the middle and near East and in ports like Alexandria, Naples and other Mediterranean cities.*

Shattuck did not know of Gerhard's work in this line and he regarded his data as too scanty to form a conclusion and so he left the question open as to whether they were two diseases or varieties of the same disease. After nearly three years abroad Shattuck decided to come home to Boston where he embarked on a distinguished career. Shattuck was made professor of clinical medicine in the Harvard Medical School and after several steps became the Hersey Professor of the Theory and Practice of Medicine, taking his place in a line of distinguished teachers that have filled that chair. Dr. Shattuck served as physician to the Massachusetts General Hospital for thirty-six years.

Besides Shattuck's contribution to medical education he did a noteworthy thing when he founded Saint Paul's School at Concord, New Hampshire. He gave his summer residence and the surrounding farm for its use. This school is one of the most beautiful in America and its chapel, with the statues of Saint Paul and Dr. Shattuck at the entrance, most impressive.

James Jackson, Jr., was one of the distinguished Bostonians to come under the teaching of Louis. He was a graduate of Harvard, A. B., 1828; M.D., 1834, but before graduation he went to Paris in 1831 and worked there, except for six months, until July 1833. He helped to form the Société Médicale d'Observation de Paris, where he was an intimate friend of Gerhard and Pennock, all protegés of Louis, and of Oliver Wendell Holmes who gave distinction to the group.

Not yet a graduate in medicine, young Jackson must have inherited some of the genius of his father who was professor of medicine in the Harvard Medical School. Jackson returned to Boston and took his degree in 1834 when he wrote an

* In this country, typhus fever has made a great increase during the last five years, especially in ten of the southern Atlantic and south central states. The U. S. Public Health Service under date of February 12, 1945 has kindly furnished the following table of cases and deaths: *1938:* c. 2294, d. 137; *1939:* c. 2998, d. 143; *1940:* c. 1882, d. 101; *1941:* c. 2787, d. 135; *1942:* c. 3736, d. 175*: 1943:* c. 4530, d. 180; *1944:* c. 5353, d. (figure not supplied).

account of the epidemic of Asiatic cholera which struck Paris in 1832. He was awarded the Boylston Prize for his essay on "Pneumonia" and he was also the first to call attention to the prolonged expiratory sound in the diagnosis of phthisis.

But it all came to an untimely end for he died of pericarditis a month after he graduated in 1834. It was a crushing blow from which his father never wholly recovered. Ten years later Prof. Jackson published the notes on sixty cases of cholera observed by his son in the wards of Paris hospitals. That was just one hundred years ago.

Another Bostonian who came under Louis's teaching was Henry Ingersoll Bowditch who was born in Salem, Mass., in 1808. He was graduated from Harvard College in 1828 and from the medical school in 1832, just in time to join the group in Paris studying under Louis. His studies covered nearly two years at La Pitié, later going to London; but he credited Paris with the better teaching. These years bore fruit and he soon made a notable contribution to medical science in the treatment of pleurisy with effusion. He did this with the help of Dr. Morrill Wyman who had invented a trocar and cannula connected to a suction pump. With this Dr. Bowditch successfully aspirated the effusion in a case of pleurisy in April, 1850, an operation which no one hitherto had the courage to perform. During ten years thereafter Bowditch operated on several hundred cases successfully. Dieulafoy, of Paris, published the description of his instrument, devised for the same purpose, about ten years after Bowditch led the way, establishing thoracentesis as one of the most beneficial measures in medical practice.

With Dr. John Ware Bowditch founded the Boston Medical Library Association in 1874. His last paper was contributed to the American Climatological Association, of which he was an honorary member, and was entitled "Open Air Travel as a Cure for Consumption" accomplished by traveling with horse and buggy through New England in 1889; and by 1892 this remarkable personage and public spirited citizen had passed away in his 83d year.

Dr. William Pepper, the first of a line of distinguished teachers of medicine, was born in Philadelphia in 1810 and took his degree in medicine at the University of Pennsylvania in 1832. Although he had planned to sail at once for France he delayed his departure until late in 1832, or early in 1833, when he went directly to Paris and returned to America in 1834. In joining the group of Americans studying under Louis he met Gerhard, Pennock and Holmes and doubtless shared their enthusiasm for their teacher. Pepper became in time Professor of Medicine in the University of Pennsylvania, dying in 1864 at the early age of 54. His brilliant son, William Pepper, also held the same chair and became Provost of the University. He likewise died too soon.

An interesting letter from Oliver Wendell Holmes dated from Boston, June 5, 1890, contains a graceful tribute to the father and his sons. I am indebted to Dr. Oliver Hazard Perry Pepper for it:—

"Dear Dr. Pepper,

Your name recalls my life in Paris where your father was one of my fellow students, since then in his life and that of his children, the name has come before me always with honorable mention as connected with important offices and valuable labors. I am much obliged to you for the pamphlets which I have read with pleasure, especially the very interesting account of Dr. Rush.

Very truly yours

(signed) O. W. Holmes

One of Louis's most distinguished pupils was Alfred Stillé. He was born in 1815, studied medicine at Jefferson College, Philadelphia, and became a resident physician at Blockley under Dr. W. W. Gerhard then fresh from Paris. Stillé was also one of those who upheld the doctrine of the distinction of typhus from typhoid. It was my good fortune to come under Stillé's teaching at the University of Pennsylvania where he held the chair of Medicine. He was a clear and forcible teacher, much beloved by students and the patron of the oldest and most highly prized medical society in that school.

Stillé was the first secretary of the American Medical Association and, later, its president and he finished his distinguished career as president of the College of Physicians of Philadelphia and a fine portrait of him adorns the hall of the College.

Another doctor and a pupil of Louis's destined to achieve great fame in medicine was Alonzo Clark who was born in Vermont in 1807, received his A.B. from Williams College in 1828 and his M.D. from the old College of Physicians and Surgeons in 1835. He was twice in Paris before 1840 and became a keen student of pathology and microscopy at a time when the microscope was

rather rarely used. As physician to Bellevue Hospital he was noted for his strict insistence on cleanliness and for treating typhoid fever and typhus with fresh air day and night. Alonzo Clark introduced the use of opium in peritonitis. He was a great teacher and a valued consultant and was undoubtedly the leading and most beloved physician of his day in New York.

One of Clark's pupils and close associates was Chauncey Leeds Mitchell who was born in Connecticut in 1818 and died in 1888. He was the son of Minott Mitchell and was a graduate of Union College. After graduating from the College of Physicians and Surgeons he became a resident physician in the New York Hospital. He went to Paris in 1837 and passed two years in France and England. His European training under Louis well fitted him as a consultant. He was an associate of Dr. G. P. Camman in the department of diseases of the heart and lungs in the Northern Dispensary of New York City. I knew him all through my boyhood and I have reason to be grateful to him for he knew me from the day I was born.

Turning southward we find two notable physicians who visited Paris in 1835 and were pupils of the medical faculty. One was William Power of Baltimore, who was born in 1813 and was a graduate of the University of Maryland in 1838. He immediately went to Paris where he spent three years studying under Louis, Chomel and Andral in the medical wards. His studies were reflected in two courses of lectures which he gave in Baltimore on physical exploration of the chest; and in 1845 he was lecturer on the Theory and Practice of Medicine; but he died in 1852 in his thirty-ninth year, cutting short a brilliant career.

In December, 1835, another southerner named John Bassett took courage and sailed on the "Roscoe," a packet ship bound for Liverpool. He was the "Alabama Student" memorialized in a delightful way by William Osler. Finally reaching Paris he found accommodations in the Place Pantheon in the Latin Quarter and he devoted himself to the teachings of Velpeau. On his return at the end of a year he recorded his impressions and in a letter he said: "When I look at some of the medical men by whom I am surrounded I blush for shame. Old men daily may be seen mixing their white locks with boys and pursuing their profession with the ardour of youth. There is not a solitary man in France that is idle; for if he was, that moment he would be outstripped."

Following the example of these early leaders there were some Americans who went to Paris for diverse reasons and sought different teachers. One of these was James L. Cabell, of Virginia, but we do not know what clinics he attended but he must have studied physiology for he became professor of that subject in the University of Virginia from which he had been graduated and a fine portrait of him is now in its library. He is said to have been one of the best teachers this famous school ever had. Other members of the group in Paris at this time were Thomas Stewardson and William Patrick Johnston. Johnston came from Savannah and took his degree of A.B. at Yale and his M.D. at Pennsylvania after which he served as resident Physician at Blockley. He then went to Paris and after three years returned to America where he became one of the founders of the pathological society in Philadelphia. He later taught surgery and obstetrics but we do not know that he came under Louis's teaching.

Stewardson, however, devoted himself to medical practice in Philadelphia where he became one of the leading practitioners.

From Charleston went Francis Peyre Porcher, a graduate of the Medical College of South Carolina, in 1844. He spent two years in France and was elected Professor of Clinical Medicine and of Materia Medica and Therapeutics in his Alma Mater. He was famous as a botanist and died in 1895, aged seventy. He and the two Gibbes and Peter C. Gaillard were fellow students in Paris, all coming from Charleston. David H. Tucker, of Richmond, is deserving of note as one of the pioneers.

Louis, after all, great teacher that he was, was only one of many French physicians and scientists who have helped to carry the lamp of learning into distant corners of the world. It was not long before Americans were seeking the clinics of the great neurologists, Charcot, Raymond, Duchenne, Dejérine, Brown-Sequard and Pierre Marie at La Salpêtrière, the great hospital for nervous diseases. Claude Bernard was making his discoveries in physiology and Pasteur was beginning that long career that was to revolutionize our knowledge of disease and point the way to its prevention. It was a French military

surgeon who first discovered the malarial organism and it was a Frenchman, Widal, who showed us how to recognize typhoid fever through the microscope. Then came the great service to humanity by the Curies who brought hope to those sorely afflicted.

What a debt we owe to France! For years she has taught us art, physical science and medicine and she has enriched the whole field of literature. She has been our constant friend withal. We comforted her in her dark days and we rejoice with her in her final triumph. The clouds have passed away and France is sunny again.

*Post Nubila Coelum.*

# Rummaging in the Museum

## V

## That Infernal Machine

## (Dr. Harrison Allen's Thoracograph)

*By* JOSEPH McFARLAND, M.D.

*Honorary Curator of the Mütter Museum of the College of Physicians of Philadelphia*

JUST inside of the door of the crowded and dimly lighted basement room in which the overflow of the Museum is stored, there has stood, as long as anybody can remember, a peculiar large and heavy apparatus that seems to have attracted very little attention except by its awkward position, which might be described as 'in everybody's way.'

The result was frequent collision, usually followed by some mild expletive when no harm was done, or a more emphatic one if damage was done or pain inflicted. By gradual evolution of language it came to be called that "infernal machine."

One of the peculiar things about it, and perhaps that which caused it to be so long neglected, is an appearance suggesting that it is intended to be used in the preparation and mounting of specimens rather than, itself, a specimen of some kind. But no one knew for what purpose it could be used, in the former case, or what it is, in the latter. The former curator disclaimed any knowledge of it; the older Fellows of the College were uninformed about it; the catalogue, recently newly written by Mrs. Ella N. Wade, the present curator, is silent about it; the "Accessions to the Museum" that used to appear on the monthly announcements of the Meetings of the College, made no reference to it, and the carefully kept minutes of the meetings of the Museum Committee contain no mention of its purchase, its presentation or, in the latter case, its acceptance. The only known fact about it is obtained from a small tag, tied to it, upon which is written "Deposited by Dr. Harrison Allen," and nothing more.

This paper is a record of various experiences attendant upon our efforts to find out what the contraption is, by whom invented, for what purpose, when, and where, and why it has become the deserted orphan in our basement.

But before what is to be said about it can be understood and appreciated, it is necessary that the reader should know what it is like.

It consists (see Figs. 1 and 2) of a heavy iron casting (a), smoothed, japanned, and daintily ornamented in what one of those who examined it calls the style of 1880 or thereabouts, having at the bottom a rather flat tripod (b) with two long feet (shown in the illustration) and a shorter one, from which arises a hollow tapering column some 2 feet, six inches in height, and about four inches in diameter at the bottom and two inches in diameter at the top. Each foot of the tripod is rounded and perforated, either to permit the attachment of casters, or to permit it to be screwed or bolted to the floor. About six inches from the top of the column there is a small cast iron wheel about eight inches in diameter (c) that actuates a pinion geared into a rod in the center of the column, by which the height of the apparatus may be raised or lowered at will, and maintained at the desired height by tightening a thumb screw opposite to the wheel. The part of the rod above the wheel is rounded and acts as a pivot about which the whole superstructure can be rotated. To the top of the projecting rod an adapter is fastened, and as it ends in two flat strips, affords opportunity for riviting the two outer plates of a large quadricircular cutter hinge, each about four inches long and two and a half inches broad. Between these, and firmly held in place by a bolt, is the third blade of the hinge (d), attached to what would seem to be the essential part of the apparatus by several small bolts. By means of this large cutter hinge the relation of the lower supporting part and the upper or essential part may be adjusted to any angle between horizontal and vertical and fixed by a thumb screw.

Supposing that the upper part of the apparatus (e) is its essential part, it is incomprehensively simple for it seems to consist of nothing more than

a large brass ring about twenty inches in diameter, made up of two thin flat bands about two inches wide and half an inch thick, carefully superimposed so as to rotate one upon the other. The inner and heavier, being firmly fixed to the supporting hinge, cannot be moved, but the outer one can be slid around it as the projecting handle attached to it (i) and shown in the illustration, is moved from side to side. Flanges above and below the outer ring, keep it from slipping out of place. There is no limit to the excursion. The ring can be moved all the way round.

There are no graduations, figures, or measures of any kind anywhere upon the apparatus.

In the under side of the inner and heavier ring, equally spaced about its circumference, are three small ball and socket joints (f), with thumb screws to tighten them. Each ball is perforated and penetrated by a brass rod (g) about twelve inches long and one-eighth of an inch in diameter. Another thumb screw determines the position of the rod through the ball. The distal end of each rod is in the form of a flat disk (h) about three quarters of an inch in diameter, and transverse to the long diameter of the rod.

The position of the joints and rods is such that they cannot be brought up on the outer side of the rings; only on the inner side.

The only movable parts of the apparatus, as we thus see it, are the rack and pinion for raising or lowering it, the cutter hinge by which it can be made to assume the horizontal or perpendicular position, the rods with their terminal discs, and the outer ring that slides about its fellow.

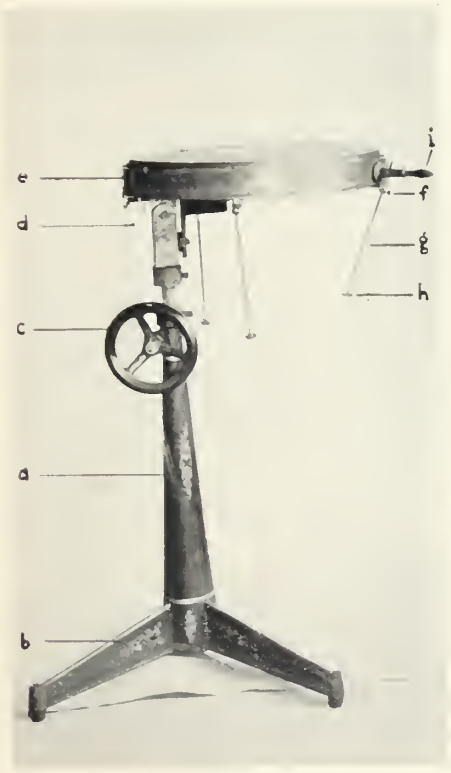


Fig. 1. Horizontal Position

Fig. 2. Vertical Position

The apparatus in the horizontal position (Fig. 1) has somewhat the appearance of a table, a metal plate having been laid upon the upper edges of the rings.

This metal plate, (shown in Fig. 2B), is almost but not quite the diameter of the brass rings, so

that it rests upon them, so insecurely that the least weight placed upon it will tip it one way or the other.

For years, in the storeroom, this disk has rested on the rings, giving the table effect, but to anyone touching the apparatus it is immediately obvious that it is simply piled there, where it does not belong.

The metal plate is circular, of aluminum or some other white metal, and about an eighth of an inch thick. The surfaces are smooth, the edges rounded. Upon one surface are three small spring clips as though to fasten down papers; on the other is what seems to be a brass reinforcing disc. It is round, fastened by eight small screw bolts, and from its center arises a half inch brass rod, two inches long with a screw thread on it.

There seemed to be no place anywhere upon the apparatus to which this rod could be screwed. This several times raised the questions, (a) whether the disc was a part of the apparatus upon which it rested, or of some other; (b) was some part of the apparatus by which the two were connected, now lost or mislaid?

As no one knew what the apparatus is or how it is used or for what purpose, these questions could not be answered.

What has been described is what anybody can see in a very few minutes if he uses both his eyes and his intelligence. Perhaps Sherlock Holmes is right when he says of his opponents, "They see, but they do not observe."

It must not be concluded that because everybody we asked disclaimed any knowledge of our "infernal machine", nobody expressed any opinion in regard to it. No indeed; quite the reverse! Opinions were so numerous, so diverse, so impossible, and in certain respects so in conformity with one another as to have afforded us much merriment, especially when expressed by some authority eminent upon something else.

One Fellow of the College descended the stairs to the basement, glanced for a moment at the machine and gravely said, "It is an apparatus for grinding teeth into thin slabs for study with the microscope."

Another said, "It is a drill for boring holes in bones when skeletons are being mounted." A third, "It is a part of a bandsaw for making sections of bones."

Now, whether a grindstone, a drill or a saw, to be of any use, in addition to the grindstone, the drill or the saw, it must have movable parts and means of acquiring some kind of power to effect their movement, which it has not.

A dentist, who carefully examined a photograph of it, thought that it might be a "dentist's table of some kind," but he did not practice dentistry, nor had he an opportunity to touch it and see that it could not be a table of any kind.

In the beginning it seemed as though we ought to be able to find out about it by devoting attention to various activities of the donor, but that turned out to be a mistake. Dr. Harrison Allen was a distinguished man in his generation. He was a first class anatomist, and wrote a very fair textbook upon that subject; he was an excellent physiologist, and for some years was Professor of Physiology in the Medical Department of the University of Pennsylvania; he was a Zoologist, specializing upon bats, upon which he published several monographs; he was a practitioner of medicine, specializing in diseases of the nose and throat, and during the latter years of his life, he was the first director of the Wistar Institute of Anatomy. He died in 1897, so that he must have "deposited" our "machine" in the Mütter Museum before that year.

In thinking it over it seemed as though the apparatus might have been useful to him as an anatomist, as a physiologist, as a zoologist or as a nose and throat specialist. I, therefore, set out to consult the oldest members of these various groups. It was hard to find any who had known Doctor Allen personally or even remembered having seen him. To have done so one would have to be about 70 years old, and men of that age in all of the enumerated specialties are few and usually retired. But I hunted up a number of the old men, none of whom could enlighten me, and then began with the younger generation, choosing, for the most part, those who are active workers and writers, and who are, therefore, supposed to be informed about instruments used in the past as well as in the present. As information was not forthcoming, I increased the scope of investigation.

Mrs. Wade, the curator of the Museum, examined the illustrations in the catalogues—especially the old catalogues—of the various instrument makers preserved in the library of the College, but found nothing resembling our apparatus.

I asked all kinds of doctors, surgeons, ophthalmologists, otolaryngologists, physiologists,—every-

body who would be kind enough to go to the basement and examine the apparatus but nobody knew what it was. As has been pointed out many opinions were expressed, and in the course of time I was amused to find that they quite regularly followed a single interesting pattern.

Thus, the otolaryngologists, never having seen anything like it among the apparatus used in their activities, conjectured that it was an optical instrument useful in mapping the eyegrounds, etc. The ophthalmologists knew nothing about it, but opined that it might be an anthropometric instrument for measuring skulls. The anatomists were sure that it was a physiological apparatus, the physiologists that it was zoological!

Where had I encountered this kind of a thought pattern before? Oh, yes! It occurs in Edgar Allen Poe's story "The Murders in the Rue Morgue." When the witnesses who heard the shrieks of the murdered woman and the conversation between the supposed murderers, one violent and with a high pitched voice, the other subdued and in low voice were being examined. In their testimony the witnesses were all chiefly concerned with the shrill voice.

Isadore Muset, a gendarme, thought "the shrill voice was that of a foreigner . . . could not make out what was said, but believed the language to be Spanish." Henri Duval thought "the shrill voice . . . was that of an Italian . . . was not acquainted with the Italian language." Odenheimer, a native of Amsterdam . . . was sure that the shrill voice was that of a Frenchman, but could not distinguish the words uttered.

William Bird, an Englishman, found "The shrill voice was very loud . . . is sure that it was not the voice of an Englishman. It appeared to be that of a German, but he does not understand German."

Alfoncio Garcio . . . is a native of Spain. "The shrill voice was that of an Englishman . . . is sure of this. Does not understand the English language, but judges by the intonation."

Alberto Montani . . . "thinks it the voice of a Russian. He is an Italian and never conversed with a Russian."

Well, I think the pattern is now clear! Each witness believed the murderer to belong to a nation, whose language he did not understand. Of course they were all wrong, for as you remember, the murderer was not a man of any nationality, but a huge ape! So it is with those who expressed opinions about our "infernal machine," they were always connecting it with some science with which they were not familiar.

The question having arisen whether the machine might not have some function entirely apart from medicine, photographs of it were taken to non-medical institutions and advice sought. At the Franklin Institute I was kindly received by the director, personally introduced to an appropriate scientist with whom I talked for some time. He had never seen anything like it, did not know what it was, but ventured the opinion that it might be a device for measuring the faces and angles of crystals. He was not a mineralogist! At the Engineering School of the University of Pennsylvania, I was led into a great room full of all kinds of machines, where I met the professor who kindly stopped his work, looked long and painstakingly at my photographs, did not know what the apparatus is, but thought it might be for the use of a photographer. He is not a photographer himself! Again the same thought pattern appears!

I next decided to see what I could find out by correspondence with other museums, and accordingly sent letters of inquiry with inclosed photographs to five of those I deemed to be the most important in the country.

The first answer was to the effect that no one connected with the institution had ever seen anything like our apparatus, but the director "thought it might possibly be a foreign body localizer to be used with x-ray." (He added that "it was simply a very wild guess," and months after, when I told him what the apparatus was found to be, he wrote, "I shall never learn not to stick my neck out by expressing an opinion on something that I know nothing about.")

From the next museum came three opinions given by three different persons:—"Might be some kind of a craniophore"; "I presume that it was devised for locating places on the head or face, but it is not the ordinary anthropometric apparatus"; "We conclude that this is an obsolete manufactured anthropometric device, discarded like the Bertillon system." From a third museum, "I guess that it is a craniophore, designed for orientating the skull."

Well, to me all of these opinions were erroneous, for the apparatus could not be made to conform to the requirements of any of them. I had, therefore, learned nothing and seemed to be at the end of my rope. Must I give it up as a bad job?

Here I found a dose of my own medicine to be extremely useful. I remembered a pet story that I for many years told my classes in order to urge them to renewed and more patient endeavor when seemingly overwhelmed by failure in some enterprise. It is not my story, but is told concerning his own disappointments in the pursuit of the probable mosquito transmitting of the parasite of malarial fever, by Major Ronald Ross.

Ross worked with Sir Patrick Manson who was the father of the theory, and who urged him to study it experimentally in India. That, Ross determined to do, and returning to his station, at once began. To make the story short, he tells us that the dissection of a mosquito for the purpose of finding the parasite, took about an hour; then he goes on "after having thus carefully dissected about one hundred mosquitoes and found nothing" . . . here is the lesson for the student and, indeed for me, for we would have said, "there is nothing in it," given up, and turned to something else, . . . "I decided that I must be working with the wrong kind of mosquito. I, therefore, transferred my attention to another common dappled-wing mosquito, and at once began to have success."

A wise man of my acquaintance once told me that "the easiest way to find out anything is to ask somebody that knows." I fully agree with him and as you see have been putting the advice into practice, but with no more success than Ross had with his first examined mosquitoes. Could it be that like him I have been investigating the wrong kind of mosquitoes? Let me try another kind!

It will be remembered that a number of those who expressed opinions thought that the apparatus might be anthropometric. I always believed them in error because in the absence of scales, divisions or other measuring devices, it seemed incapable of subserving such purposes. Furthermore, it assumed that the apparatus was a table, and that the rods with their disc-shaped ends were placed in contact with a skull laid upon it. The apparatus is not in any sense a table, and the rods cannot be made to touch anything placed on the disc that makes it resemble one.

But a professional anthropologist might know more than the volunteers, or might know of some similar apparatus. I, therefore, consulted a good friend at the University of Pennsylvania Art Museum, showed him the photographs, and explained what has been told here. He listened, examined, pondered, then remarked that he was not a "physical anthropologist" and that if this be an anthropometric apparatus, it is out of the scope of his knowledge. He vouchsafed no suggestion as to its uses, but advised me to go somewhere where there would be a good anthropologist and anthropometrist, recommending the Wistar Institute as the place where I would probably find one. Following the suggestion I immediately called upon my friend, the director, Dr. Edmond J. Farris, showed my photographs and explained my predicament. He proved to be exactly the right kind of mosquito!

To my astonishment, my delight, and then to my disappointment and amusement, Farris no sooner looked at the photograph than he said, "Yes, I know what this is; it is *an apparatus for measuring the respiration.*"

"*For measuring the respiration!* Oh, no, Dr. Farris, you were never further from the truth than now!"

Look at the absurd position in which I stood; I had not the slightest idea what the apparatus was, or what it was for, and now, after prolonged effort I have found a man who *does know* and *tells me, and I don't believe him!* Human frailty! I here and now make my apology to you, Dr. Farris, for thinking it possible that you could be as ignorant and as stupid as myself!

But there is no doubt of Dr. Farris' correctness. He not only knows what the infernal machine is, but *he has one!* Yes, indeed, stored in a lumber room on the top floor of the Wistar Institute there is an identical apparatus that dates from the time of the administration of Dr. Harrison Allen as its director. By comparison we found that our apparatus was imperfect. The circular metal plate does belong to it, but the means of attaching it is gone, and the most essential part of all, the pantograph was missing.

When Dr. Allen left the Wistar Institute, he explained to his successor, Dr. D. Milton Greenman, all about the apparatus and many years afterward, when Dr. Greenman was leaving, he explained it to Dr. Farris, who now conferred this hereditary information to me.

Figure 3 is a photograph of the Wistar Institute apparatus, completely set up and ready for use. By means of a heavy bracket attached to the outer ring, the metal disc has become a table adjoining the rings. Another light bracket, also attached to the outer-movable-ring, supports the

pantograph, which is the long slender metal bar that terminates at the left in a vertical point, and at the right hand end in a small, freely movable, toothed wheel. This end of the pantograph arm is kept directed toward the center of means of the projecting handle, the whole of the apparatus just described proceeds to travel in the same direction, and the metal plate by contacting with the stationary inner brass ring is made to rotate in the same direction.

FIG. 3

(Courtesy of Edmond J. Farris, Ph.D., Director, Wistar Institute of Anatomy and Biology, Philadelphia.)

*The Wistar Institute Thoracograph, Complete in All Details*

The metal disc is now found, indeed, to be a table, but in an unexpected position. A bracket not seen in the illustration is firmly screwed to the inner—immovable—brass ring, into which screws the rod with the thread for which no use could be found, to hold the disc firmly in place. Our bracket, having been detached and put in another part of the store-room, was not supposed to belong to the apparatus, but when found, was easily fitted in place.

Upon the inner ring is another bracket (a), that supports the arm (bc) for tracing the outline of the thorax at (c) and drawing upon the card at (b). This arm, that might be called the *pantograph,* has been removed from our apparatus and lost, but shows well in the photograph.

the large rings by means of a fairly strong coiled spring.

One very important fact is that the edge of the metal plate rests upon the top edge of the inner—immovable—ring. This determines that when the outer—movable—ring is pushed to the right by

The purpose of the apparatus is to draw outlines of the chest wall upon a card or paper fastened to the surface of the disc by its spring clips.

To use it, it is first made to assume the vertical position; the patient, nude to the waist, stands in front of the top part, which by means of the rack

and pinion is raised high enough for the top to be returned to the horizontal position without the rings touching the head. When this has been achieved, the three rods, with their disc ends are adjusted so as to touch the skin, and afford the patient the means of maintaining a constant position. Either a blank card upon which a pencil in the pantograph can write, or a smoked card or paper upon which the point can write is prepared, and the pantograph arm is adjusted so that the toothed wheel contacts with the chest wall. By now taking the handle and rotating the whole around the patient, the notched wheel follows the contour of the chest wall and transmits it to the point or pencil, by which it is made to appear on the paper. Various modifications made in the recording accomplish different ends. Thus in deformed thoraces such as occur in scoliosis, kyphosis, tuberculosis, aneurisms or after surgical operations, an outline of the chest may suffice; but if the freedom of respiration is to be recorded, one outline showing inflation and another in complete deflation may be made upon the same paper.

It is interesting to see how men's thoughts move in correspondence with the subjects chiefly engaging them. To a doctor of medicine most interested in pathology, the purposes that the apparatus could accomplish are enumerated above; to Dr. Farris, essentially a biologist, its chief important purpose was to assist in classifying animals of the same kind according to the bodily habiti occasioned by the relative excesses or deficiencies of certain internal secretions. This difference of opinion is important. Was the apparatus designed for the one purpose or the other? For what still other purpose may it have been originally devised? By whom? When? Where? What, if anything, did it succeed in accomplishing? Why has it been abandoned?

Dr. Farris did not know what the apparatus was called, so that it could not be easily found in the literature. I supposed it might have been known by some such name as thoracometer, and set out to see what could be found under that and similar words. Mrs. Wade, on some other tack, was the first to find something—a cyrtometer,—described by Dr. Robert Potter Elmer, resident physician to the Free Hospital for Poor Consumptives at White Haven, Pa., for measuring the curves of the body. He employed it for the differential measurement of the chest halves. It in no manner resembled our apparatus.

I found, after long search, a paper in Spanish, —"Thoracograf," by Dr. Vergara Lope, published in the Gaceta Medica de Mexico, 3rd series: 4: 760: 1909, that seemed to be a review of observations made by Hall, Dufestel and Gueneau de Mussy. There is a somewhat lengthy description of the apparatus they used, and there are frequent references to the illustrations which seem to have been omitted. However, what they used was not like our apparatus, for the outline of the chest was given as a series of pin pricks.

I think that it was in the answer to our letter to the Smithsonian Institution that we first learned that our instrument is probably correctly called a *thoracograph*. But after all our trouble in trying to find out what it is, it was interesting to have a member of our own Museum Committee, who had frequently been asked to look at it, but never "found time," walk up to it one afternoon and instantly say, "that is a thoracograph."

While pursuing the subject through the literature I came across a paper by C. von Heimleth, who said, "The anomalies of position and the changes in the form of the trunk arouse interest, from the scientific point of view, in the anthropologist, the internist and the surgeon, but are of special interest to the orthopedist." In the course of his paper he refers to another, "Om den habitula skoliosens behandling medels mekanisk gymnastik," by Dr. G. Zander of Stockholm, published in Nordiskt Medicinisk Arkiv 21: No. 22: 1–21: 1889. In this paper, there is an excellent illustration of a large and much more complex apparatus than ours, but which may very well be its prototype. That the Zander apparatus was known in the United States during Dr. Harrison Allen's time there can be no doubt, for Dr. Herman Nebel in the Zeitschrift f. Orthöp. Chir. **2**: 334: 1892, refers to two that were in Baltimore, one in New York and one in St. Louis in 1892.

Who modified the Zander apparatus to the simplified state represented by the two in Philadelphia (if they be modified Zander apparatus) and whether it was done to adapt them to the requirements of the anthropologist, the internist, the surgeon or the orthopedist, it has not been possible to find out. I could find no papers published in the United States that mention it in praise or

dispraise. Perhaps some reader of these lines may be able to help us. If he can and will do so, we shall be greatly obliged to him.

We have several times been asked why all this trouble has been undertaken, and why we have worried our friends about what is obviously a piece of junk. Those who said it, belonged to that same group that has surprisingly declared that the Museum is full of junk! Perhaps so, but what is a museum for if not to cherish and display both the successes and the failures of those who earnestly endeavor to advance science?

And now that we know our apparatus to be a Thoracograph, it has become too dignified any longer to be spoken of as *that infernal machine*, or to be kept in the basement store-room. It has been moved into the museum proper and holds a place of honor! Thoracograph!

# Memoir of Karl Kornblum

*By* EUGENE P. PENDERGRASS

DR. KARL KORNBLUM was born in Evansville, Indiana, on March 19, 1893, and died at the University Hospital in Philadelphia on May 16, 1944, at the age of 51, after an illness of only a few hours. The immediate causes of death were a cerebral thrombosis and a coronary thrombosis. Prior to this Dr. Kornblum had been ailing for several years from hypertension.

Dr. Kornblum came from the middle west, and he inherited the characteristics of his forbears which provided him with a level head and common sense, which in him were augmented by a kindliness of nature that endeared him to his friends and colleagues.

After graduating from the University of Indiana in 1916, Karl Kornblum obtained his degree in Medicine from the University of Pennsylvania in 1919. After two years interneship and one year of residency in obstetrics at the Hospital of the University of Pennsylvania, he turned his talents toward surgery, and rose to be chief of the Outpatient Department of the University Hospital during 1923 and 1924.

In 1925 Dr. Kornblum went into private practice, but soon gave that up to return to the University Hospital where he became associated with the late Dr. Henry K. Pancoast. There he remained until 1933 when he resigned to accept the Directorship of the Department of Radiology at the Graduate Hospital. In 1938 Dr. Kornblum resigned from the Graduate Hospital to accept the chair of Radiology at Jefferson Medical College, vacated by the late Dr. Willis F. Manges. He held that chair from 1938 to 1942. He returned to the University of Pennsylvania in January, 1943, as Clinical Professor of Radiology and Associate in the Department of Radiology of the Hospital of the University of Pennsylvania, where he remained until his death.

Dr. Kornblum was one of those rare individuals who had a gift for teaching, and although he has done a considerable amount of clinical investigation and published many articles, he will be remembered long for his teaching ability. He had the rare gift of keeping the attention of his students. Because of this ability he was called upon to give a great many lectures at home and abroad, and he was constantly preparing for these lectures, the preparation of which was not a chore but a source of relaxation.

In reviewing the contributions of Karl Kornblum one finds it difficult to evaluate which will live longest, but it is universally agreed that his contributions to the urinary tract during the early investigations of Uroselectan and other media, and his contributions to the respiratory tract, will continue to be informative to those going into the specialty of radiology.

In 1925 Dr. Kornblum married Miss Mabelle Edwards, who has always been a most sympathetic and devoted wife. They have two lovely girls, Joan who is 16 and Ann who is 14. It is my impression that their home life has been most unusual and extremely happy.

Karl Kornblum had no particular hobby except that he enjoyed his family, his work, and his friends. Consequently he spent a great deal of time with his family in traveling and at home and they, like those of us who worked with him, are going to miss him exceedingly.

Karl Kornblum held the following appointments in the University of Pennsylvania prior to the time he became a Professor at Jefferson Medical College: Instructor of Surgery, School of Medicine, 1922–1929; Assistant in Research Medicine, School of Medicine, 1923–1924; Instructor of Radiology, Graduate School of Medicine, 1927–1934; Instructor of Roentgenology, School of Medicine, 1929–1930; Instructor of Radiology, School of Medicine, 1931–1933; Assistant Professor of Radiology, Graduate School of Medicine, 1934–1938; Director, Department of Radiology, Graduate Hospital, 1934–1938.

He was President of the Philadelphia Roentgen Ray Society 1933–1934, and was a member of many scientific societies. In all of these societies he participated in their scientific deliberations.

As a physician and a man Karl Kornblum was unusually gifted. Even though he must have had knowledge of his impending catastrophe, none of us who worked with him knew anything about it.

He was a man in every sense of the word, and has fully justified the confidence which his teachers, colleagues and friends entrusted to him. As time passes, many will arise to try to fill his place, and it can be said without qualification that any man who can combine those rare attainments possessed by Karl Kornblum of being a brilliant teacher, an excellent clinical investigator, and a man of unquestionable integrity, should be most happy.

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# Observations on the Diagnosis of Coronary Disease[1,2]

*By* CHARLES C. WOLFERTH, M.D.

*Professor of Clinical Medicine, School of Medicine, University of Pennsylvania*

IT IS stated on the basis of the causes of death reported in the obituary column of the Journal of the American Medical Association that at the present time about 25% of physicians die from coronary disease. This condition is not merely the most frequent cause of death but in many instances it produces a long period of disability or illness prior to death. There is no more challenging problem before us than its conquest. Essentially it is the problem of atherosclerosis because most coronary disease is a result of atherosclerosis of the cornonary arteries. Only during recent years have we begun to see more clearly the nature of the problem and its magnitude. In the past a more or less fatalistic attitude was adopted concerning arteriosclerosis as though the days of an artery were numbered from the beginning. There are good reasons for questioning this point of view and particularly so in the case of atherosclerosis which in some animal species can now be produced experimentally by a variety of measures (1). Moreover the fact that a perversion of metabolism such as uncontrolled diabetes mellitus can accelerate its development in humans should encourage us to think that it may be possible to discover some vital link in the chain of events that leads to atherosclerosis in non-diabetics. Although we are still much in the dark so far as its fundamental etiology is concerned, coronary disease presents certain special problems with respect to diagnosis and treatment. No attempt will be made here to deal with them in a systematic manner and thus repeat much of what is found in text books and special articles. Rather than that I hope to supplement and sometimes question the text book ritual.

[1] Mary Scott Newbold Lecture LV, the College of Physicians of Philadelphia, April 4, 1945.

[2] From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

## Clinical Diagnosis

As one studies the literature bearing on the diagnosis of coronary disease and contemplates the status of the subject to-day, he is forced to the conclusion that (1) certain clinical manifestations of that disease are many times more frequent than they were in the past, or (2) our predecessors and the older among us were singularly blind to some of them such as acute coronary occlusion. It may be that both are true. So far as angina pectoris is concerned, Heberden (2) described its symptoms so clearly that since his time little has been added to that picture beyond a few minor details. More than thirty years after his first report he was able to assert that he had seen over 100 cases of which three were women, an average of approximately three cases per year including one woman every ten years. There could be little reasonable doubt as to Heberden's ability to recognize angina pectoris. It seems fair to assume therefore in view of the amazingly few cases he saw that no matter

what the incidence of coronary disease may have been, angina pectoris was not as frequent in London in the latter part of the 18th century as it is in Philadelphia to-day.

The possibility of sudden death in an anginal attack was recognized long ago. Pathologists found bony hardness of the coronary arteries in such cases and learned that in some individuals infarction may result from coronary obstruction. Nevertheless the clinical concept of acute coronary occlusion had a long and difficult struggle for existence. Not even the excellent clinico-pathological study by Leyden (3) nor the much later paper by Obrastzow and Straschesko (4) made a lasting impression. Herrick's (5) first paper in 1912 met a similar fate. About this time, however, clinicians began to manifest some interest in electrocardiography. Smith (6) in 1917 showed that experimental ligation of coronary vessels was followed by electrocardiographic changes. Herrick (7) in 1919 published another paper on clinical coronary occlusion and in 1920 Pardee (8) described some of the electrocardiographic changes that may occur in humans during the acute stages of myocardial infarction. By this time, interest in the subject began to establish itself and there has been a continuous stream of literature ever since. It would appear therefore that electrocardiography can claim some credit for the eventual widespread recognition of a form of illness that only a few of the more observant clinicians had recognized without its aid.

Years ago it seemed worth while to emphasize that one's "index of suspicion" for coronary disease must be high in persons over forty. In recent years it appears to be manifesting itself much more frequently at even younger ages. The frequent presentations and voluminous literature dealing with the disease and the universal experience of physicians in seeing their colleagues and patients succumb to it so frequently have apparently raised our indices of suspicion to a sufficiently high level. It is probable at present that in the Philadelphia district, more errors are being made on the side of diagnosing coronary disease when it is not the cause of the patient's symptoms than in failing to recognize its presence when it is responsible. If we are to diagnose it accurately we must familiarize ourselves with the symptoms and signs it can produce and must become equally expert in the recognition of all the other conditions that may simulate it. The consultant in heart disease is apt to see more brachial and intercostal neuritis than the neurologist, more esophageal spasm than the gastro-enterologist, more of the scalenus anticus syndrome than the surgeon, and more peri-arthritic conditions involving the shoulder regions, particularly on the left side, than the specialists on arthritis. He is also likely to see myriads of persons with aches in the left chest, the causes of which he is often unable to determine precisely, although in many, evidences of overstrain and/or psychoneurosis may be detected.

It is useful to classify the clinical manifestations of coronary disease into four categories, namely those of (1) abnormal cardiac mechanisms, (2) angina pectoris, (3) acute coronary occlusion, and (4) cardiac failure. These may occur singly or be associated in various combinations or various sequences. The types of symptoms which may occur in each of these categories is fairly characteristic but they may be mingled in the patient's mind with concurrent symptoms caused by other conditions including psychoneurosis. In eliciting the history one must insist on learning the details of symptoms. Thus in angina pectoris in which the diagnosis has to be made almost entirely on the basis of history, this principle is all important. The distress must centre within certain limits, it has certain routes of radiation, it is constricting, burning, boring, or stretching and in its areas of radiation sometimes aching and often as my former associate Col. Francis C. Wood used to emphasize, the patient has trouble trying to find a word to describe it. When patients say that it is a sharp pain, they usually mean severe. It is probably never lancinating or pricking. It builds up to a climax and decreases gradually. It rarely lasts less than a minute and the severe part of the attack rarely persists beyond ten or fifteen minutes. It is characteristically excited by exercise and more readily just after eating. It begins during or immediately after exertion and not some time later. It may also be excited by sudden chill of the body surface, mental perturbation or when one is in the recumbent position. Patients are more comfortable sitting than lying when they have the distress. It is often relieved almost immediately by belching. It is relieved at least in part within one to two minutes by amyl nitrite or nitroglycerin. If any of a patient's symptoms conform to criteria such as those outlined above, it is almost certain that he has angina pectoris, no matter how many psychoneurotic disturbances may be present at

the same time. On the other hand, a patient may have frequently recurring pain in the chest and definite evidences of heart disease, but if the pain does not conform to the criteria for angina pectoris, it is not angina pectoris but caused by something else.

The distress of acute coronary occlusion does not have such clearly defined criteria by which it can be diagnosed as does angina pectoris, but the areas of distribution and types of distress are similar. Although the diagnosis in some cases seems quite easy, in others, it is difficult and not infrequently, can not be made with certainty. There is an indefinite dividing line between the clinical syndromes of angina pectoris and acute coronary occlusion. Angina pectoris is in all probability not infrequently initiated by clinically unrecognized occlusion of a small coronary artery. Thus, damage to the myocardium can sometimes be demonstrated by electrocardiography early in the course of the anginal syndrome, with subsequent reversion to a normal tracing, in spite of persistence of attacks of distress. The gradual closure of a coronary vessel may be accompanied by classical brief anginal seizures as well as by repeated attacks each long enough in duration to suggest acute closure of an artery. This syndrome would doubtless be included in what certain writers now call coronary insufficiency. Moreover, acute obstruction of a vessel may be accompanied by severe pain but by no subsequent developments suggesting myocardial infarction. The evidence of the necropsy table demonstrates that in many cases the number of coronary vessels obstructed, far exceeds the number of attacks that had produced symptoms. There can be little doubt that, as in the case of occlusion of arteries of the legs, coronary artery occlusion is often symptomless. It is probable that under such circumstances, occlusion is usually a gradual rather than a sudden affair.

If the diagnosis of coronary disease is to be made at the earliest possible stage, one should not concentrate his attention entirely upon the anginal syndrome. As a matter of fact, a large proportion of cases of coronary disease run their entire course without any of this group of symptoms and finally die of cardiac failure resulting from gradual deterioration of the heart muscle. It might be said that coronary disease marches on relentlessly toward cardiac failure and that disturbances of cardiac mechanism, angina pectoris and acute coronary occlusion may be accidents along the road. The earliest symptom may be merely fatigability or a gradual realization on the part of the patient that he does not feel as well as he had in the past. He may observe that he is a little more short of breath on exertion than formerly, he may begin to note palpitation or there may be at times a vague sense of discomfort in the chest or epigastrium. Slight attacks of vertigo are sometimes the first symptom. A little tightness of shoes at the end of the day or swelling of ankles may be observed. When such complaints can not be accounted for readily on other grounds, one should not fail to think of the possibility of coronary disease.

Acute coronary occlusion may sometimes come like a bolt from the blue, but this is not so frequent as is generally believed. It is often possible by digging into the history, to elicit one or more of the complaints mentioned above or transient attacks of what the patient may have regarded as indigestion, but which were in reality so-called pilot attacks of angina pectoris. The latter often preceded an attack of acute coronary occlusion by a few days or weeks. Acute occlusion is more apt to come without previous warning following such episodes as acute upset of the gastro-intestinal tract with vomiting and/or profuse diarrhoea and also following unaccustomed strenuous physical exertion.

Paroxysmal cardiac dyspnoea is often stated to be a symptom of onset of coronary disease. This may be true following running for a train, shoveling snow or other violent exertion, gross indiscretion in food intake, or when it is precipitated by the inception of an abnormal rhythm with rapid ventricular rate. Rarely in our experience, this syndrome rather than the anginal type of pain may mark the onset of acute coronary occlusion. As a rule it is possible to elicit symptoms prior to the onset of the first attack of paroxysmal cardiac dyspnoea, when that condition results from coronary disease.

Physical examination may afford some clues as to the possible presence of coronary disease. Although it is well recognized that either intimal or medial types of arteriosclerosis may be spotty in their distribution, there can be little doubt that the individual who shows evidences of arteriosclerosis in vessels accessible to examination, is more liable to have also atherosclerosis of his coronary arteries. In the diabetic, in whom the peripheral vascular lesion is presumably sometimes at least partly atherosclerotic the frequent associ-

ation with coronary disease is well recognized. The recent demonstration by Hueper (1) that in the experimental production of atherosclerosis by the injection of methyl cellulose, focal and sometimes extensive hyalinization and calcification of the media may be produced, and that occasionally lesions resembling closely the Monckeberg type of calcification of the media result at positions isolated from the intimal lesions, suggests that intimal and medial forms of arterial involvement may not be so different in etiology as is sometimes thought. It is a good clinical rule to think of the possibility of coronary disease not only in the diabetic but whenever anything suggesting disturbance of cholesterol metabolism is found. This should include annulus senilis, xanthomatous deposits including even the small ones about the eyes, hypothyroidism and diseases of the liver or biliary tract. Coronary disease as a pathological finding has been reported in young individuals with lipoid nephrosis. Perhaps tobacco stained fingers should now suggest disturbance in cholesterol content of the blood. Hueper (1), after reviewing the changes in blood cholesterol observed by Strauss and Scheer (9) in heavy smokers and in animals exposed to nicotine over long periods, makes the following statement: "These observations suggest that in chronic nicotinism, a cholesterogenic atheromatous factor may complicate the primary vasospastic action of the alkaloid."

Coronary disease should be thought of as a possible part of the vascular involvement in the patient who begins to age rapidly or prematurely. The appearance of abnormality of cardiac mechanism, even such an ordinarily trivial disturbance as extrasystoles may signal its presence. The finding of a systolic apical or aortic murmur not previously observed, changes in auscultatory characteristics of the first or second sound or unexplained narrowing of the pulse pressure may occur in patients with coronary disease before symptoms make their appearance.

In the majority of cases requiring serious consideration of the diagnosis of coronary disease, one may apply his best efforts along clinical lines and still have little reason to feel entirely satisfied with the information he has elicited. He can sometimes obtain further help from radiographic methods which by now should be classed as a part of the technique of inspection, not to be neglected in any case. In general however, more information as to the anatomical state of the myocardium can be obtained by electrocardiography than by any other procedure. The issues at stake make obvious the need for accurate diagnosis in coronary disease. Because of the importance of electrocardiography in that diagnosis and because of the lack of widespread understanding of its principles, I propose to devote the remainder of this discussion to it.

### Electrocardiographic Diagnosis

Those of us who have worked with electrocardiography for many years cannot justifiably flatter ourselves at the speed with which it came into its own in the diagnosis of myocardial damage. Engelmann (10) in 1873 showed experimentally that abnormal patterns could be produced by acute injury of the heart. The same phenomenon was studied by others, including Burdon-Sanderson and Page (11), Waller (12) and Bayliss and Starling (13). All these contributions seemed to have been long forgotten and those who returned to the subject after Einthoven devised the string galvanometer do not even mention them. Fifty years ago, had any one familiar with both Leyden's and Bayliss and Starling's work become inspired with enough curiosity to take electrocardiograms in a few cases of the type described by Leyden and used the precordium-right arm lead recommended by Bayliss and Starling, he would have realized quickly that he had stumbled onto something interesting. However, there were no portable electrocardiographs in those days, the few machines in existence being in physiological laboratories.

Perhaps the main reason why we physicians have had so much difficulty with the concepts of electrocardiography which have been taught and discussed in the literature is not because they are so complicated but because we are not trained in physics and its nomenclature. If we could think of potential of cardiac origin at a body area in terms of temperature fluctuation above or below the constant temperature of that area and the electrocardiograph as a ruler to measure the differences in the fluctuations between two areas, we might not have so much trouble. Thus when the potential at one area rises 2 millivolts and that of another area falls 2 millivolts at the same instant, there will exist at that instant a difference of potential of 4 millivolts between the two areas. If we use the conventional polarity and place the exploring electrode on the first area and the electrode with which it is paired on the second area, the electrocardiographic curve will at that instant

be 4 centimeters above the base line because the machine is so adjusted that 1 millivolt of difference of potential is reflected by a deviation of 1 centimeter. Thus if we place the exploring electrode on an area whose potential variation from the base line at any instant is designated X and pair it with one on an area whose potential variation is designated Y, the difference in potential is X − Y. If this is a plus quantity the deflection will be above the base line and if it is a minus quantity, the deflection will be in the opposite direction.

With these few simple facts, we are in a position to see why Einthoven's famous law that lead I + lead III = lead II must be true. If we designate the potential of the right arm, left arm and left leg as X, Y and Z respectively, then lead I = Y − X, lead II = Z − X and lead III = Z − Y. If we add leads I and III or Y − X and Z − Y we obtain Z − X which is the same as the value of lead II. Such relationships would have to exist among any three points on the body. To discover the differences in potential among them, it is necessary to take only two leads instead of three. This law of Einthoven's merely expresses an identity.

Einthoven (14) formulated another concept which is not nearly so simple. It is based on a series of assumptions, the most vital of which have never been proven. This is the equilateral triangle hypothesis. It has reigned supreme in electrocardiography for over thirty years and a large part of the theoretical superstructure of the subject is erected upon it. In other words, electrocardiography, so far as the theory of limb leads is concerned, is founded largely upon faith rather than reason. To find a parallel situation one would probably have to go back to the science of the middle ages or look for a similar situation in the field of the supernatural where an entire system of theology may be erected upon certain faiths.

Entirely aside from the theory of Einthoven's limb leads, they possess some practical value in demonstrating the presence of myocardial injury. This would be true of any series of leads from widely separated body areas. Pardee's (8) observation of certain changes resulting from acute myocardial infarction was confirmed by other observers and in the course of a few years Parkinson and Bedford (15) and Barnes and Whitten (16) had established the criteria by which anterior and posterior locations of infarction could be recognized on the basis of limb lead patterns. It was obvious to all working in this field, however, that electrocardiography was a hit or miss procedure, although frequent repetition of tracings was helpful. We were often humiliated when we followed our cases to the necropsy table, to find extensive cardiac injury that we had failed to discover in electrocardiograms. Many felt that something needed to be done about it but we had no good idea what it should be.

In our laboratory we knew that earlier workers had used chest leads and following Lewis' example, we sometimes used an antero-posterior chest lead to demonstrate auricular activity when limb leads were unsatisfactory for that purpose. Bayliss and Starling's precordium-right arm lead had passed over our heads completely. We had not been impressed in 1929 as much as we should have been by Otto's (17) demonstration that by pairing both electrodes on the front of the chest, underlying experimentally produced cardiac injury was revealed. One of the most interesting studies to appear about that time was Feil and Siegel's (18) demonstration that certain patients with angina pectoris showed significant electrocardiographic changes more or less coincident with the attack. We (19) were able to confirm this finding in a series of thirty patients. One half of them showed significant changes in the limb leads during an attack. We then showed that somewhat similar changes could be obtained by temporarily clamping the coronary arteries in dogs and cats. By this time the chain of evidence to indicate that angina pectoris was due to temporary insufficiency of coronary blood flow to a part of the heart muscle seemed fairly complete. At least the long controversy which had continued practically up to then, stopped.

On review of the data referred to above it was noted that every time arteries supplying the posterior wall of the heart were clamped, changes developed in limb leads but that when arteries supplying the anterior parts were obstructed, little change occurred that could be regarded as significant. This behavior suggested that by opening the chest the front of the heart had been more or less insulated from the extremities. It was found on further investigation (20) that even when good contact was maintained between the front of the heart and the extremities, limb leads still failed to reflect satisfactorily deprivation of blood supply to the anterior wall of the heart.

At this point we were about ready to abandon the investigation. We felt that some contribution had been made to knowledge of the mechanism

of angina pectoris because of the similarity of changes in patients and those produced by temporary obstruction of a coronary vessel, and that disturbance of blood supply in some parts of the heart were reflected better in electrocardiograms than disturbance in other parts. It was decided, however, to do a few final experiments, placing electrodes directly on the heart muscle to note whether deprivation of blood supply caused a different type of change in the patterns of potential on the anterior wall than elsewhere on the ventricular surface. It was quickly discovered that spectacular injury currents developed following deprivation of blood supply to any part of the ventricles. Such a finding indicated that the trouble with electrocardiography must be that the methods of making leads was inadequate. It was then a simple matter to show that if an electrode were placed over the precordium, deprivation of blood supply to the anterior wall of the left ventricle could be reflected just as consistently as involvement of the posterior wall could be reflected in leads II and III. The leads developed in this experimental work were then tested in clinical electrocardiography and in 1932 cases were reported in which a chest lead clearly demonstrated the presence of infarction of the anterior wall of the left ventricle when Einthoven's limb leads failed to do so (21).

Shortly after our first paper on the use of chest leads in the study of acute coronary occlusion, F. N. Wilson and his co-workers (22) demonstrated independently that chest leads could be used to determine the side of the lesion in bundle branch block. During the next few years numerous publications appeared on the use of chest leads and it was universally recognized that they had helped to make electrocardiography a far more useful diagnostic procedure than it had been previously.

In contemplating the evolution of various advances in electrocardiography, the value of study of the patterns developed at cardiac surfaces becomes apparent. Lewis (23) was the first to realize the importance of placing one electrode on the heart and the other electrode elsewhere. By so doing he was able to follow the course of the excitatory process throughout both the auricles and ventricles. We had noted how readily abnormal injury currents recorded from the anterior wall of the left ventricle are also present in leads made with an exploring electrode on the anterior chest wall. Wilson had shown the value of comparing cardiac surface and precordial leads in experimental bundle branch block.

The ultimate objectives of clinical electrocardiography began to clarify themselves as soon as it became apparent from experiment what advantages exploration of cardiac surfaces possessed over exploration of body surfaces. The problems were (1) to discover the significance of deflections obtained by placing an exploring electrode on cardiac surfaces and the changes produced by various forms of cardiac injury, (2) to find how potential variations were distributed from cardiac surfaces to body surfaces, and (3) to devise a method or methods by which potential variations of cardiac origin developing during each heart beat could be recorded in electrocardiograms without material distortion. Once these three objectives were achieved, it would become a relatively simple matter to discover what leads would be most favorable for clinical electrocardiography so that the empirical, hit or miss nature of the procedure could be overcome.

A complete explanation of the mechanism of development of patterns of potential variation at cardiac surfaces must await further knowledge of the nature of the bio-electric phenomena associated with excitation of the single cell. This is a problem for bio-physicists rather than students of clinical electrocardiography. Osterhout (24) has made recent important contributions to this phase of the subject. He has emphasized not only the change in permeability of the cell membrane and the migration of $K^+$ ions from the inner to the outer wall of the cell when excitation begins but the importance of what he calls "R" substance as essential factors in the development of potential changes at the surface of the cell. For the present we shall probably have to be content with the idea that the sharp drop in potential at cell surfaces at the beginning of excitation is associated with the migration of $K^+$ ions from the inside of the cells to those surfaces and that the T wave is associated with the re-entry of these ions to the interior of the cells.

Although it was long recognized that the QRS complexes reflected the spread of the excitatory process throughout the ventricles, the most notable contribution to our understanding of this group of deflections was Lewis' (23) recognition of the intrinsic deflection. This is a sharply negative deflection always present in the QRS complex when the exploring electrode is placed on a cardiac surface either epicardial or endocardial. It reflects the arrival of the excitatory process at the surface under the electrode. At epicardial surfaces this deflection is always preceded by a

positive pre-intrinsic deflection which reflects the passage of the excitatory process from the endocardium to the epicardial surface underlying the exploring electrode. The remaining parts of the QRS complex, which precede and follow these two deflections reflect activity in other parts of the heart. On the endocardial side, the intrinsic deflection was found to occur quite early, usually very near the beginning of the QRS complex. The intrinsic deflection was the landmark used by Lewis in the study of the course of the excitatory process referred to above. However, his recognition of the cause of this deflection was probably an even greater contribution so far as the future of electrocardiography was concerned.

Wilson and his co-workers (25) extended our knowledge of patterns of potential variation near the heart. Their work on bundle branch block constituted an extension of Lewis' (23) observation that when bundle branch block was produced experimentally, the arrival of the intrinsic deflection on the ventricular surface of the side of the lesion was delayed. Their important original observation was that a deflection corresponding to the intrinsic deflection could be recorded from the overlying precordial surface. They found that the T wave at epicardial surfaces tended to be upright. When an exploring electrode was placed within a ventricular cavity, the QRS complex was simple in form, consisting mainly of a downward, followed by an upward deflection although occasionally the downward deflection might be preceded by a very small upward deflection. The T wave with the exploring electrode within the ventricular cavity was inverted. Wilson and his coworkers observe that when infarction of the myocardium is produced experimentally, the pattern of the QRS complex obtained with the exploring electrode placed over the infarcted area may be converted to the pattern of the ventricular cavity with a large early downward deflection. The reason for this is death of the tissue directly under the electrode so that it now taps the endocardial pattern of potential variation. These workers also observed that the main pre-intrinsic deflection which forms a peak with the intrinsic deflection is much smaller in amplitude over the right ventricle than the left, presumably due to the lesser thickness of the right ventricular wall. They also stated that "if the subendocardial muscle of some part of the ventricular wall passes into the active state earlier than the subendocardial muscle which lies between the exploring electrode and the ventricular cavity, the initial negativity of the cavity is transmitted to the electrode and a Q deflection occurs." (25) It seems probable that this view is correct. However, in the exploration of some canine hearts a Q deflection cannot be obtained anywhere over the surface of either ventricle (26). This suggests that the negativity of the cavity is not unopposed and that at times it may be overbalanced at the epicardial surface. This subject requires further investigation.

We can summarize the chief pathological changes in the QRS complex as follows: (1) Changes due purely to intraventricular conduction defect. The time required for the complete excitation of both ventricles can be measured by the duration of the QRS complex. Prolongation of that interval beyond the upper normal limit marks the presence of intraventricular conduction defect somewhere in the ventricles. Its location can be detected by observing the time relations of the intrinsic deflection at various epicardial areas with reference to the beginning of the QRS complex. If there is a conduction defect in a part of the ventricles ordinarily activated early, considerable delay in the arrival of the excitatory process at that area may occur without prolongation of the QRS complex. Thus a QRS complex of normal duration does not necessarily exclude an intraventricular conduction defect. (2) Changes due to injury of the myocardial wall. Under such circumstances there may also be localized injury of conduction tracts at the site of the lesion. This may help to produce a Q wave when an exploring electrode is placed over the injured area but actual destruction of the fibres composing the ventricular wall which are responsible for the pre-intrinsic and intrinsic deflections causes potential of the ventricular cavity to continue to be transmitted to the exploring electrode with little interference.

*The RS-T segment.* Following the QRS complex and preceding the T wave electrocardiograms made with the exploring electrode placed over healthy heart muscle as a rule show but little potential variation from the base line. If, however, an area of heart muscle is injured by trauma, cautery, deprivation of blood supply or by the application of various chemical solutions or drugs, positive RS-T segment displacement is recorded when the exploring electrode is placed over that surface. In our second set of experiments on temporary deprivation of blood supply to certain parts of the ventricles (20), it was noted that over uninvolved parts of the heart surface, what would now be called negative RS-T segment displacement was sometimes re-

corded. This observation enabled us to predict in our first clinical paper on chest leads (21) in 1932 that the RS-T segment displacement in chest leads of posterior infarction should be opposite in direction to those of anterior infarction. This prediction was confirmed later in the same year (27).

We returned to this problem recently (28) with the purpose of testing a working hypothesis to the effect that when positive RS-T segment variation was produced over injured muscle, negative variation would be produced over uninvolved areas. We were moved to test this hypothesis not only by the observations mentioned above but by the following: (1) The negative RS-T segment displacement recorded in chest leads in lateral infarction of the left ventricle which we had described in 1938 (29). (2) The negative segment displacement produced in chest leads by digitalis considered in connection with the observations of Barnes and his co-workers (30) that digitalis affects chiefly the endocardial aspects of the ventricular wall. (3) The limb lead patterns recorded by Boyd and Scherf (31) after traumatizing the endocardial wall of the left ventricle. (4) The fact that during the QRS complex negative potential variation at the endocardial surface produces positive potential variation at the overlying as yet unactivated epicardial surface. All of these observations suggested that the direction of current flow between injured and uninjured regions and activated and inactivated regions is such as to cause these opposing directions of potential variation. It was found by experiment that the production of positive RS-T segment variation at epicardial surfaces, provided the area were sufficiently extensive, was accompanied by negative variation in the ventricular cavities and that extensive injury of the subendocardial muscle or the injection of KCl solution deep into the myocardium produced negative variation at the epicardial surface. The production of positive variation at one part of the epicardial surface was accompanied by negative variation elsewhere on that surface. It was therefore possible to formulate the generalization that the finding of positive RS-T segment displacement when an exploring electrode is placed on a ventricular surface indicates the presence of injury directly under the electrode and that the finding of negative displacement indicates the presence of injury at either the opposite side of the wall or some other part of the ventricular myocardium. Other findings in this investigation, the significance of which is not as yet clear were as follows: (1) Certain procedures which produce RS-T segment displacement affect the amplitude of the intrinsic deflection of the QRS complex or the shape and direction of the T wave or both whereas the other procedures, such as the application of extremely weak ouabain solution to the epicardial surface seem to produce only RS-T segment displacement. (2) During the recovery period of the myocardium positive displacement may temporarily change to negative displacement just prior to the disappearance of the injury current.

*The T wave.* Comparatively little has been learned about the T wave from study of its behavior at cardiac surfaces. As stated above, the deflection is supposed to be positive when an exploring electrode is placed on the epicardial surface and negative within the ventricular cavity. Its direction and shape may be changed by such a slight effect as exposing the cardiac surface to room air (32). Under such circumstances the T wave may not only become inverted in epicardial leads but upright in endocardial leads (27).

So-called unipolar leads and leads in which the potential variations transmitted to the exploring electrode dominate the pattern. This is one of the most difficult and at the present time most controversial subjects in electrocardiography. I am unable to discuss it entirely apart from distribution of potential at body surfaces which is to be presented below. About the only point on which general agreement can be obtained is that leads such as those discussed in the previous paragraphs in which one electrode is placed on a part of the heart and the other elsewhere are essentially unipolar leads. The reason for this is that potential fluctuations at cardiac surfaces are so much greater in magnitude than those at a distance, that the latter have little influence on the pattern which is in effect the potential transmitted to the exploring electrode. No such happy set of circumstances exists, however, when both electrodes must be placed at a distance from the heart. Wilson and his co-workers (33) have pointed out that if the Einthoven equilateral triangle hypothesis be valid, the mean potential variations of the right arm, left arm and left leg must always equal zero. They have devised a central terminal, connected it with the three extremities and paired it with the exploring electrode. They called the leads obtained in this manner, unipolar

leads. The only thing still necessary to do before these unipolar leads justify their flattering name is to establish the validity of all the assumptions which underlie Einthoven's hypothesis, including those stated by him and those which he did not recognize. Others have claimed that by immersing the body surrounded by a network in a salt solution bath unipolar leads can be obtained by pairing the exploring electrode with the network, because under these circumstances the potential of the network remains constant (34). It is easy to demonstrate that the reasons advanced to prove that the potential of the network remains constant are not in accord with established laws of physics (35).

Several years ago we instituted some simple experiments to test the probability of accuracy of Wilson's unipolar leads in recording the potential variations of the extremities (36). We assumed as a working hypothesis that at positions so far from the heart as the surfaces of the proximal and distal parts of the attachment of an arm, the patterns of potential variation should be similar, although at the proximal position the magnitude of the variations should be larger because this position is nearer the heart. Thus, by pairing electrodes on these positions with the exploring electrode nearest the heart, one should be able to record a pattern of difference of potential similar to the actual potential variations of the arm itself, although no evidence could be expected as to the magnitude of the potential variations of the arm. Somewhat to our amazement, the patterns of difference of potential recorded across the attachment of the right arm usually bore no resemblance to Wilson's unipolar leads of the right arm, although on the left side, there was sometimes a certain resemblance. These results must mean that either something was wrong with our working hypothesis or Wilson's unipolar leads, a matter which seemed to demand further investigation. The next step (37) was to carry the exploring electrode to positions successively nearer the border of the heart on the same side, keeping the other electrode on the original position. This procedure on the right side did not materially change the pattern to positions so near the heart as the C-1 or even C-2 position, although the nearer the exploring electrode was placed to the heart, the larger became the deflections. A similar relationship was found to exist on the left side sometimes as near the heart as the C-5 position. These observations seemed to be in accord with the hypothesis that the patterns of potential variations of the arms are similar to those of certain positions much nearer the heart but that they undergo decrement in their magnitude as distance from the heart increases. Such an hypothesis however could not be reconciled with the Einthoven equilateral triangle hypothesis because Wilson had previously shown that potential of a precordial position corresponds to that of the underlying epicardial surface. According to our new hypothesis therefore the potential variations of each arm would have to be dominated by the results of electrical activity in a limited part of the heart. According to Einthoven's view, every part of the heart is far enough away from an extremity that electrical activity in all parts is equally capable of registering effects in the extremities.

If the distribution of potential variation from the right and left borders of the precordial area to the homolateral arm is as our experiments seemed to indicate, it becomes possible, provided decrement is sufficiently great, to find three areas along a line radiating from the heart, having the relationship that the potential variations of the proximal area are equal to the sum of the potential variations of the two distal areas. Having found such areas, an exploring electrode can be paired into this electrode system in such a way that the potential transmitted to the other three electrodes is neutralized except for potential variations that might be distributed uniformly throughout the upper extremity. By this means a closer approximation to the potential variations of the exploring electrode can be recorded than by other methods. The evidence to support these statements has been fully covered elsewhere and need not be repeated here (37). By the use of this procedure it was found that the potential variations of the right scapular region are relatively negligible in magnitude and that by pairing the exploring electrode with one placed over this area, essentially the same results are obtained as with the more complicated method (38).

*The distribution of potential at body surfaces.* I have already pointed out that certain methods of pairing electrodes along lines extending from just outside precordial regions to the attachments of the arms indicate that the pattern of potential variation of the right arm resembles that of the C-1 position (which we have called the C-1 pattern) and that of the left arm closely resembles that of a chest position just outside and often slightly

above the apical region (called the extra apical pattern). Similar results are obtained when the exploring electrode is paired with one placed over the spine of the right scapula (38). Probably because the arms are much farther from the heart than the chest positions, the deflections are much smaller in amplitude. The decrement on the right side is considerably greater than on the left, also probably because of the greater distance involved on that side. The distribution of potential below the diaphragm in some respects seems different from that above. In the rat, potential patterns of the liver, intestines, abdominal wall and legs were found to be practically identical indicating a remarkably uniform distribution. In a single canine experiment potential patterns of areas of the under surface of the diaphragm directly under the heart showed some differences at adjacent areas. Over all other parts of the diaphragm, the interior of the abdomen, the abdominal wall and legs, the pattern was practically the same. There was decrement on the diaphragm as distance from the heart increased but very little decrement below the diaphragm all the way to the legs. In the human we had no opportunity to study the potential patterns that develop on the under surface of the diaphragm. However, an excellent opportunity presented itself to study the potential patterns of the esophagus, stomach, duodenum and jejunum and compare them with the patterns of the lower part of the trunk and legs (39). The tracings obtained with an exploring electrode in the lower end of the stomach, duodenum and jejunum were in most instances practically the same as those of the legs and usually there was practically no decrement as distance from the heart increased. This pattern we had previously designated the diaphragmatic pattern because of the probability that it is derived from electrical activity of the part of the heart in contact with the diaphragm. When the exploring electrode was located in the fundus of the stomach or the lower end of the esophagus, the deflections tended to be larger and the pattern correlation although definite, was not so close. At the auricular level of the esophagus the pattern was of the endocardial type which supports Brown's (40) suggestion that the potential of the ventricular cavity is transmitted to the electrode at that level of the esophagus. It is perhaps of some interest in this connection that in the course of the study on RS-T segment displacement referred to above, positive displacement was recorded with the exploring electrode at the auricular level both in a hypertensive and a patient fully digitalized when other leads showed negative displacement.

The orderly distribution of the three patterns of potential referred to above, each to a large section of the body, is totally different from what would be expected if the Einthoven equilateral triangle hypothesis were valid. In fact, the practically uniform distribution of the diaphragmatic pattern over large parts of the body below the diaphragm alone is enough to controvert the hypothesis. Nevertheless, a number of observations were made to ascertain what results could be obtained by using Wilson's unipolar leads to study distribution of potential (35). By this method, no correlation was obtained between patterns recorded with an electrode on the $C_1$ position and on the right arm. As the electrode was moved successive steps from the former to the latter position, the change in pattern was gradual. On the left side however, the correlation was better, although not so good as when the exploring electrode was paired with one placed over the spine of the right scapula. The most illuminating comparison of the results of the two procedures was in right bundle branch block. Wilson (41) had noted a number of years ago, when comparing the potential pattern of canine right bundle branch block recorded from the right ventricle and from the right side of the precordium, that the latter included a sharp downward deflection early in the QRS complex, not present in the truly unipolar lead from the surface of the right ventricle. He observed a similar deflection in human right bundle branch block. This he called "the unexplained deflection". We (35) were able to confirm Wilson's finding of the unexplained deflection in leads from the right side of the precordium made according to his method. This unexplained deflection was not present in leads made by our method but in other respects the QRS patterns were not dissimilar. As the exploring electrode was moved from the right side of the precordium by successive steps toward the right shoulder and then onto the right arm, our procedure showed preservation of the pattern but decrement in magnitude of deflections as distance from the heart increased. Wilson's method showed decrement in all parts of the QRS complex except the unexplained deflection, which was just as large on the arm as over the right side of the precordium. On the basis of this behavior,

Wilson's unipolar lead is presented with a dilemma. If the unexplained deflection does not undergo decrement because it is derived from his central terminal, the method does not produce unipolar leads. If, on the other hand, the unexplained deflection is transmitted to the exploring electrode, it does not undergo decrement as distance from the heart increases which is not in accord with Einthoven's vital assumption that the trunk functions as a homogeneous fluid volume conductor. Wilson's unipolar lead under these circumstances would be based on an hypothesis that is not valid.

In positions close to the heart such as the precordial areas, there can be little doubt that the surface patterns are largely dominated by electrical activity in the part of the heart nearest to them. This is the reason why the pattern is likely to show considerable change when the exploring electrode is moved a relatively short distance. However one is never able to record such abrupt changes in exploring the precordium as can be done on the epicardium when the electrode is moved from a sharply defined area of injury to healthy tissue.

*Clinical Applications.* The developments reviewed above may be wearisome to the physician whose interest lies in what electrocardiography will tell him about the state of the heart muscle of his patients. As a matter of fact, this has been the chief interest and objective of our group of workers during our long struggles. It now seems clear that the two principles which should guide us in selecting positions for the application of electrodes to patients are the following: (1) The exploring electrode should be placed on all positions where experience has indicated that significant changes in patterns of potential variation are best exhibited and (2) the electrode paired with the exploring electrode should be placed on a position of relatively slight potential variation so that the old handicap of electrocardiographic curves, namely that they represent the difference between two unknown variables can be overcome as far as possible. These principles are in direct opposition to the Einthoven concepts of electrocardiography and the issue must be sharply drawn between them.

Wilson and his school (25) have made notable contributions to our understanding of precordial leads and there is no serious conflict between the views developed by him and our own concerning the significance of the deflections in those leads. Such differences as do exist we hope to point out in a future publication on this subject. The main point clinically on which all must agree, once they know the reasons for it, is that a single precordial lead is hopelessly inadequate. The patterns formed at the right ventricular surface must be studied by leads made with the exploring electrode placed on the overlying right side of the precordium. The patterns formed at intermediate positions where both ventricles contribute are also essential. Moreover, the exploring electrode must be placed on the left side of the precordium including one position at least slightly beyond the left heart border. If one wishes to make the minimum number of precordial leads that are essential, he can use either the $C_2$ position or one midway between $C_1$ and $C_2$, $C_3$, $C_4$, and $C_5$, and in cases with cardiac enlargement to the left, the $C_6$ position. Our experience has indicated that almost nothing of value is elicited by including other precordial positions.

Precordial leads yield information about the patterns formed on the anterior surface of the ventricles and to some extent the lateral wall of the left ventricle. What therefore can be done to discover something about the electrical activity of other parts of the ventricles? There are only two other patterns that we have been able to find in leads made on surfaces accessible to exploring electrodes. One of these is the highly important diaphragmatic pattern. It can be obtained with the exploring electrode in the gastrointestinal tract from the stomach on down, on the surface of the trunk below the umbilicus (a level at which precordial potential has undergone sufficient decrement not to interfere) or either leg. A leg is a convenient place to attach an electrode and will serve well. The other pattern which as yet has received almost no study is the endocardial pattern obtained with an exploring electrode at the auricular level of the esophagus. Thus far all that has been shown regarding the pathological changes that may occur in this pattern is that (1) RS-T segment displacement may be positive when it is negative in certain precordial leads and (2) the T wave which is normally inverted at that level may become upright there when it is inverted in certain chest leads (26). Further study may show that this lead is unnecessary but the data available at present do not permit any conclusion about it. Leads in the esophagus below the auricular level are not recommended since contributions are

received from both the endocardial and diaphragmatic patterns. It is easy to study the transition from one pattern to the other as the exploring electrode is withdrawn a short distance at a time from the stomach to the auricular level of the esophagus.

What can now be said about Einthoven's famous limb leads? So far as leads 1 and 3 are concerned, the patterns which compose them can be recorded singly with minimal interference so that there now seems little reason beyond long established custom to make these leads. The time-honored concept of axis deviation will have to go by the board if they are not made, but electrocardiography would benefit rather than suffer from this loss. At least we would be stimulated to search for more dependable criteria for hypertrophy of one or the other ventricle. Lead 2 can be used to demonstrate the diaphragmatic pattern of potential because the right arm is a region of only slightly more potential variation than the spine of the right scapula. The CR leads serve very well to demonstrate the precordial patterns of potential.

Much has already been written regarding pathological changes in the CR precordial leads and lead 2. There would be little point in trying to include all that material here. I wish therefore to limit the discussion to points which I think have either been overlooked or not sufficiently emphasized.

I have indicated above in the discussion of the formation of the QRS complex at epicardial surfaces, that it is possible for intraventricular conduction defect to be present without abnormal prolongation of the QRS complex. For example, the anterior surface of the right ventricle is a part of the heart usually activated relatively early. Thus the intrinsic-like deflection recorded from the right side of the precordium falls quite early in the QRS complex and normally precedes by about 0.02 second the onset of the intrinsic-like deflection derived from the left ventricle as recorded from intermediate positions. Possibly the reason for this is that the wall of the right ventricle, being less thick, is traversed more quickly. When however the deflection from the right side lags behind that of the left by an appreciable interval such as 0.02 second or more, it is possible to say that there is at least a slight intraventricular conduction defect on the right side even though the QRS complex is not prolonged (Figure 1). Likewise, if the lag of the intrinsic-like deflection as recorded from intermediate positions is found to be 0.05 second later than the analogous deflection derived from the right side, it is probable that a localized conduction defect exists on the left side.

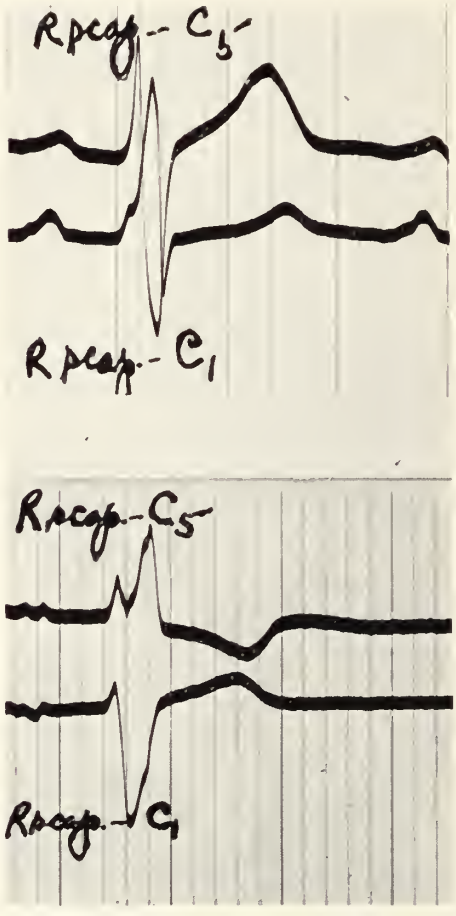


FIG. 1. In the upper illustration, two leads were made simultaneously with exploring electrodes on C-1 and C-5 positions, and both paired with an electrode placed over the spine of the right scapula. Note that the intrinsic-like deflection recorded from the C-1 position falls approximately 0.06 second after the beginning of the QRS complex and 0.03 second after the intrinsic-like deflection recorded from the C-5 position. These time relationships indicate pathological delay in excitation of the anterior surface of the right ventricle. In the lower illustration, made by the same method, the intrinsic-like deflection recorded from the C-5 position falls approximately 0.07 second after the beginning of the QRS complex and 0.05 second later than the intrinsic-like deflection recorded from the C-1 position. These time relationships indicate pathological delay in the excitation of the anterior surface of the left ventricle.

Another type of conduction defect that may be missed if multiple chest leads are not made is one

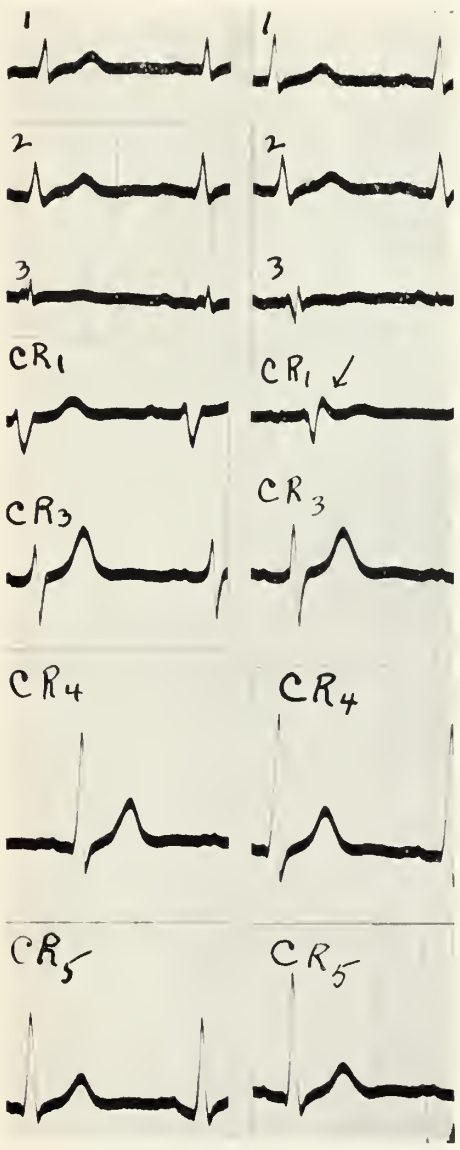


FIG. 2. Electrocardiograms of the same patient made approximately one year apart. In the CR-1 lead of the group on the left side the duration of the QRS complex is 0.13 second whereas in other leads of both electrocardiograms it does not appear to exceed 0.08 second. This finding indicates that intraventricular conduction defect in an area relatively small in extent, located elsewhere than on the anterior wall of either ventricle had developed in the interval between the recording of the two electrocardiograms.

in which a small broad final deflection of the QRS complex, which brings its duration into the pathological range, can be detected in only a limited precordial area (Figure 2). In this event the location of the conduction defect is probably elsewhere than directly under the electrode and the amount of tissue activated late is so slight that its electrical activity is capable of registering appreciable effects on the potential of only limited parts of the front of the heart. Such deflections are occasionally registered at only one or at most two precordial positions, being unrecognizable in leads made from other positions.

The initial portion of the QRS complex is the key to the detection of minor pathological changes involving localized areas of the cardiac wall aside from those lesions which involve conduction tracts of considerable size. The matter would be less complicated if a small Q deflection were not a normal finding in many persons in leads made from the left side of the precordium and also in lead II. In patients with left ventricular hypertrophy these Q waves may be of relatively large amplitude, as much as 5 or 6 mm. or even more without reflecting the presence of actual damage to the myocardium so far as we know. In such instances, however, the pre-intrinsic and intrinsic-like deflections are also large. When the Q wave begins to be disproportionately large or broad in the precordial leads or lead II, one should suspect trouble. The pattern of Q wave change in a series of precordial leads, when no single lead considered by itself could be regarded as definitely pathological, may be significant. Thus, the Q wave may make its appearance in a lead as far to the right of the precordium as CR-3. If so, it becomes progressively larger as the electrode is moved to positions further to the left until the cardiac border is passed, where all the deflections tend to become smaller. Any deviation from this pattern is likely to reflect the presence of localized myocardial damage. Thus, if the Q wave is larger in CR-3 than in CR-4, or if the ratio of amplitude of the Q wave in CR-4 to the pre-intrinsic-like deflection is greater than in CR-5, it is probable that localized damage is present (Figure 3).

The major lesions caused by coronary disease such as myocardial infarction following acute coronary occlusion, are usually not difficult to recognize, although it must be remembered that the characteristic evidences of infarction may be slow in developing and do not necessarily make their appearance coincident with the attack of pain. It is now possible to say with considerable

confidence that if significant positive RS-T segment displacement develops in a precordial lead, a part of the myocardial surface in close relationship with the exploring electrode is involved, irrespective of involvement elsewhere (26). If the displacement is negative in that lead, either the endocardial aspect of the ventricular wall or some part of the epicardial surface not in close contact with the diaphragm is involved.

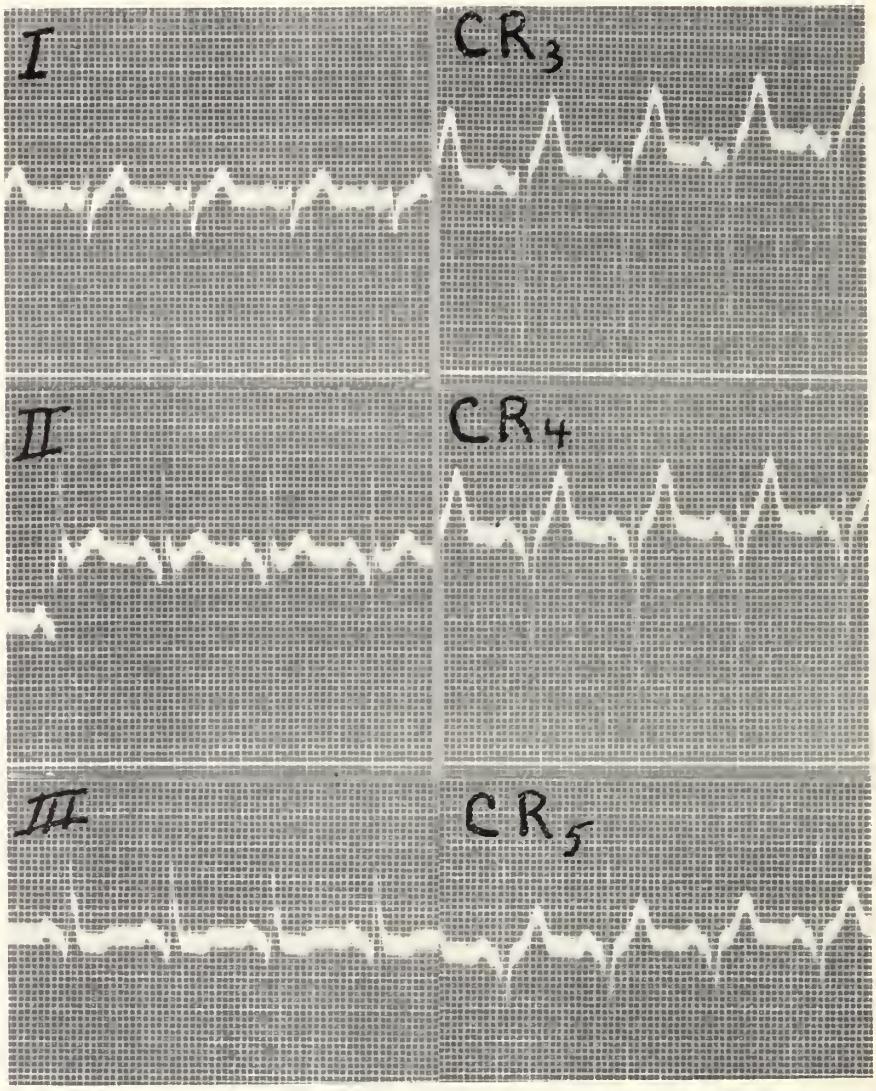


FIG. 3. (Courtesy of Dr. Joseph Edeiken). Note the absence of a Q deflection in lead CR-3 and the fact that it is greater in amplitude in CR-4 than in CR-5. Such a pattern reflects pathological change in the heart. If the amplitude of the Q deflections in CR-4 and CR-5 were reversed, there would be no definite evidence of cardiac damage.

If, however, the RS-T segment displacement is negative, either the endocardial aspects of the ventricular wall or some part of the epicardial surface not directly under the electrode is involved. Moreover, if the displacement is positive in lead II, the epicardial surface of that part of the ventricles in close relationship with the diaphragm is involved. The essence of the differentiation between acute pericarditis and acute infarction is that in the former with its usual widespread involvement there tends to be positive RS-T segment displacement both in the precordial leads and lead II. This is unusual although not impossible in the case of

infarction. However, it would be almost inconceivable to have such an extensive acute infarct without the subsequent development of pathological changes in the QRS complex. This does not occur as a result of pericarditis with only subepicardial myocardial inflammation.

The interpretation of T wave changes in electrocardiography is often a difficult and troublesome matter. The shape and direction of this deflection is influenced so readily by relatively trivial disturbance that frequently too much is read into such electrocardiographic changes. They occur not infrequently in nervous individuals with a tendency to tachycardia without any evidence whatever of myocardial damage. They are readily produced by a variety of substances such as digitalis, quinidin, nitrites, epinephrin or potassium. In experimental work, as stated above, even cooling the surface of the heart to room temperature may invert the T waves. It was observed long ago that drinking a large amount of cold water has an effect on them (42). They may become deformed temporarily during the recovery period following exertion. Superficial subepicardial involvement of the muscle such as occurs in pericarditis may cause spectacular deformity of the T waves which may persist for a long time, even years. It is probable that subendocardial involvement also changes their shape at epicardial and body surfaces. Aberrant intraventricular conduction may cause them to become inverted. They are frequently inverted in some of the precordial leads when there is hypertrophy of one or the other ventricle. In fact, over the right side of the precordium they are frequently inverted in adults with normal hearts, whereas in children with similarly normal hearts, they may be inverted as far over to the left as the C-4 position.

In spite of what has just been said, T wave changes may constitute a valuable part of the electrocardiographic picture of myocardial injury. When they are the sole evidence of myocardial abnormality one must be especially cautious in their interpretation. They form in association with certain changes in QRS complexes, definite patterns that furnish strong evidence of cardiac damage. Thus, the combination of a significant increase in the depth or breadth of the Q deflection in lead II associated with inversion of the T wave is excellent evidence of a lesion. The same is true in precordial leads except that for some reason not yet explained, the major changes in T waves are likely to be found at precordial positions further to the left than the major changes in the QRS complexes.

The patterns of T wave change in multiple precordial leads are sometimes helpful in recognizing the presence of a lesion when any single one of the precordial leads could not be regarded as definitely abnormal. Thus in normals, over intermediate precordial positions, the T wave in our experience is never smaller in amplitude than in adjacent positions on both sides of it. Any such interruption in the normal pattern of change from position to position is therefore strong evidence of a localized cardiac lesion even though the relatively small T wave considered alone would be regarded as having normal amplitude and shape (Figure 4).

### The Correlation of Clinical and Electrocardiographic Diagnosis

The fact that so much more space has been devoted in this presentation to electrocardiographic diagnosis than to what can be learned from the history and conventional methods of physical examination is in no sense to be regarded as an attempt to attach exaggerated importance to electrocardiography. The sole reason for this division is that the other procedures are well known and despite the voluminous literature of electrocardiography, its principles are not widely known and understood. After all, this procedure is nothing more nor less than a special method of physical examination, just as the use of the stethoscope or fluoroscope are special methods. A diagnosis made on the basis of an electrocardiogram alone is as incomplete a diagnosis as if it were made on the basis of the urine examination alone. One who is seriously crippled by coronary disease may have a normal electrocardiogram. It would be the height of absurdity to say that the coronary arteries or the heart itself are normal, because the electrocardiogram is normal. On the other hand, of two men with practically identical pathological changes in the electrocardiogram, one may be free from symptoms, able to carry on his work without difficulty, and the other may be a complete cardiac invalid.

In view of the frequency of coronary disease, it might properly be argued that every man over forty and all hypertensives and diabetics of any age or either sex, should be examined and have an electrocardiogram made at frequent intervals in order to detect the first evidences of a cardiac

disorder. With the new machines already practically perfected that are to come on the market after the War, it will be no more time consuming or difficult to make an electrocardiogram than a complete blood count. This procedure must not replace a careful history and physical examination. It should merely supplement them in order that one may properly assess all available data in his effort to arrive at a correct diagnosis. One warning is necessary. Much psychic trauma is being inflicted on patients by erroneous interpretation of electrocardiograms and the diagnosis of heart disease on the basis of findings that do not warrant it. It is very difficult sometimes to remove the anxiety neurosis caused by such a diagnosis. Moreover even when heart disease is present and the electrocardiogram reflects it, one should in the last analysis place weight on his clinical judgment and not too much on the results of the electrocardiogram in deciding how sick his patient is. Many a man with evidences of extensive damage in his electrocardiogram lives longer than some of his presumably healthy friends.

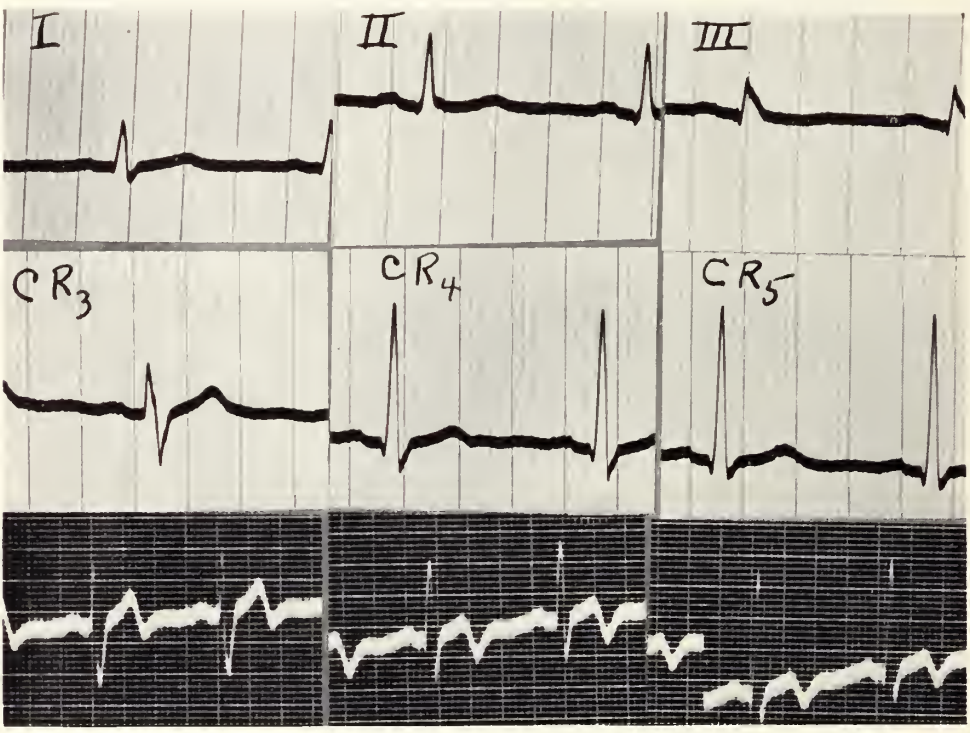


FIG. 4. Note that although the lead labelled CR-4, considered alone cannot be regarded as abnormal, the T wave is smaller in amplitude than in CR-3 and CR-5. The pattern for the three positions, however, is definitely abnormal. The three lower strips were the same chest leads made by Dr. Joseph Edeiken several months previously, when there was unquestionable evidence of myocardial damage.

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# The Early Diagnosis of Carcinoma of the Uterus*

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## Introduction

THE clinics established by Dr. Catharine Macfarlane of your city for the regular and frequent examination for women, regardless of whether cancer is suspected or not, have given great impetus to the interest in the early diagnosis of cancer. Her work and her reports have been stimulating to those of us who are interested in curing women of uterine cancer. Dr. Macfarlane is responsible for my being here tonight as speaker before your Society and I am offering to you what I consider a satisfactory method of approach to early diagnosis.

With the present methods of diagnosis at our disposal the diagnosis of carcinoma of the uterus should be made much earlier now than it could have been made a number of years ago. The only methods available at that time were the history, the feeling of the lesion on digital examination, and the appearance of the tumor and specimen on gross examination. A little later, microscopic examination of tissue removed by biopsy became possible. Today more methods are in use and these should be utilized in a routine fashion as follows: the history should be taken first, then a vaginal smear should be made before any intravaginal examination is done. After examination, including palpation and inspection, there should be observation with the colposcope, followed by a painting of the cervix with iodine—the Schiller Test. After this has been done a biopsy should be removed from the most suspicious areas suggested by the Schiller Test and the colposcopic examination. Endometrial biopsy should be considered but this test is of value only when the specimen removed is reported positive for cancer. The last procedure should be a curettage of the endometrium and an excision of a specimen from the cervix for microscopic examination in the laboratory. All the above methods are important and those of us interested in early diagnosis should be able to use each office, hospital, and laboratory procedure; these are very essential in carrying out a proper and satisfactory investigation.

*History.* The most important symptom of the history in the diagnosis of carcinoma of the cervix is the type of abnormal bleeding. "Spotting" is particularly characteristic; by "spotting" is meant bleeding between periods without any apparent reason. Blood found on underwear, and blood found on the nightgown or on the bedclothes constitute a very real suggestion of the presence of carcinoma. Bleeding after intercourse or intravaginal douching is of extreme importance; if a patient does have this complaint one must rule out carcinoma by all the available tests. Carcinoma of the cervix rarely causes an interference with normal menstrual cycles. The bleeding that occurs is usually of the kind that appears between normal cycles, or possibly there may be a little increase in the normal amount of flow. In carcinoma of the cervix secretion—or leukorrhea—frequently precedes bleeding because of the proliferative mass that is present. As ulceration or break-down of tissue takes place bleeding occurs. Traumatization causes pieces of tissue to break off and bleeding from that area of tumor. In carcinoma of the endometrium bleeding does not follow traumatization from intercourse or from douching. In carcinoma of the endometrium the menstrual cycle may be larger and longer, and in carcinoma of the cervix the bleeding is more likely to be in between the periods. There is some possibility of making a differential diagnosis between carcinoma of the cervix and carcinoma of the endometrium by the type of bleeding. Carcinoma of the cervix is more frequent in younger patients from the ages of 30 to 50, whereas carcinoma of the endometrium usually occurs in patients who have passed the menopause. Randall (1) has shown that women

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who have carcinoma of the endometrium usually have a delayed menopause or an abnormal amount of bleeding at the time of the menopause.

After the history is taken the next step is to take a *vaginal smear*. Vaginal smears were first used in the diagnosis of carcinoma of the endometrium or carcinoma of the cervix by Papanicolaou and Traut (2). Various corroborative articles have been written from other clinics. One by Meigs, Fremont-Smith, Graham, Rawson, and Kapnick (3) from the Massachusetts General Hospital helps to prove their contentions. All investigators agree that cells from the tumor are cast off into the vagina; these cells can then be picked up by a suction pipette and placed on glass slides and stained, and the diagnosis may be made from the appearance of the individual cells. Carcinoma of the cervix of the differentiated type is more easy to diagnose than the undifferentiated type. The chances of making a proper diagnosis in carcinoma of the endometrium are not so great as in carcinoma of the cervix. In our Laboratory at the Massachusetts General Hospital the latest statistics show that the percentage of error in the diagnosis of carcinoma of the cervix is not over 4, whereas in carcinoma of the endometrium it is at least 10 per cent. This error in a patient with cancer may be due to the fact that the tumor does not exfoliate, or it may be due to the error of the technician who reviews the slides. If a diagnosis of carcinoma of the cervix is made by vaginal smear it is up to the surgeon and pathologist to prove that carcinoma is not present. Investigation of a very careful sort should be undertaken.

It is essential that the laboratory technician be a trained cytologist; a great deal of study must be spent before the various cells found in vaginal smears can be interpreted. One of the greatest problems confronting us at the moment is that of diagnosing correctly, by this method, those tumors that have been radiated. In this group there is a very definite amount of confusion. Interpretation of cells from radiated tumors has not been satisfactorily worked out as yet so that a vaginal smear reported as positive following radiation may be a mistake. A biopsy, which may be difficult to obtain, must be done; the percentage of error will be much greater than in the non-radiated cases. In the early diagnosis of cervical cancer the vaginal smear is of greatest value in suggesting to the surgeon or gynecologist that something is amiss with the cells of the vagina and that thorough investigation should be carried out. Biopsy is an adjunct to the vaginal smear and is the next step to be undertaken when a smear is positive. Cervical or endometrial biopsy can be false negative because the tumor area is not always biopsied. The chances of mistakes in vaginal smear diagnosis are much greater per slide than that of tissue diagnosis because in the vaginal smear single cells can be overlooked, whereas in the Pathology Laboratory if a specimen shows no carcinoma it is because there is no tumor in the section removed. It is interesting to note that in some of our cases the diagnoses by means of vaginal smear have been more correct than those by biopsy of the cervix. In two cases of "carcinoma in situ" the vaginal smear was positive while the biopsy diagnosis was equivocal in both. In a patient with a pyometrium the diagnosis was missed by the Pathology Laboratory, not because they missed the tumor but because the curettings did not reveal cancer, yet the vaginal smear was positive and at operation the patient had carcinoma of the endometrium. There are other cases that could be quoted. If the biopsy is equivocal or if it is suggestive of carcinoma while the vaginal smear is positive, then the chances are that carcinoma is present.

*Examination* should follow, and not precede, the vaginal smear because the vaginal smear must be taken before any lubricant is spread in the vagina. On digital examination of the cervix in early cases of cancer one often feels an apparently perfectly normal cervix. If bleeding has taken place this does not exonerate the cervix; further examination must be undertaken. If, on examination, bleeding follows the finger's touch it can be assumed that there is something friable present and that the chance of there being a new growth is great. Often in patients with carcinoma of the cervix a large, cauliflower, proliferative growth can be made out; the cervix may be extremely hard or the tumor may have grown onto the vaginal wall; and there may be a certain amount of stiffness and hardness of the tissues of the cervix and the vagina. Frequently the disease extends from the cervix onto the vaginal wall. On examination by rectum there may be an extension lateral to the cervical segment; the finding of a broad utero cervical segment is very suggestive of carcinoma—whether it be of the cervix or the endocervix. The uterus containing carcinoma of the endometrium may simply be much larger than the normal one

and completely symmetrical; in advanced disease it may be completely fixed. In carcinoma of the cervix there is often fixation of the uterus or fixation of the cervix in such a way that it cannot be moved. Further advance will show extension onto the vaginal wall, into the broad ligament, and even into the ureteral, low iliac, or obturator lymph nodes which can be easily palpated. On palpation, even in the very earliest cases, a "sandy" feeling of the cervix, such as feeling sand paper or feeling graphite paper, may indicate that carcinoma is present. If a smooth, slippery cervix is felt, it usually means that a simple laceration is present. If, on inspection of the cervix, there is a lack of pink, squamous epithelium covering the cervix up to the os the lesion may be benign. This appearance may be due to a congenital erosion of the cervix or to an old laceration. An ulcerated break in the mucous membrane may or may not mean that malignant disease is present; a raised area which bleeds on touch is often diagnostic; a cauliflower mass on the cervix or of the cervix proves to the examiner that malignant disease is a definite possibility. Tuberculosis of the cervix which is extremely rare might cause confusion. Ulceration, easy bleeding, a "sandy" feeling and raised areas should attract attention to the possibility of the presence of carcinoma of the cervix. In carcinoma of the endometrium there may be a perfectly normal, small uterus, or there may be a large uterus—much larger than one would expect in a patient at the time of the menopause. A large uterus with abnormal bleeding is very suggestive of carcinoma of the endometrium in the patient beyond the menopause.

Next in the examination the *colposcope* should be used. The colposcope and its use has been very well described by Hinselmann of Hamburg; his colposcope is a heavy, expensive, and clumsy instrument. I have used a colposcope in my office since 1933 and never in those 12 years have I ever made a diagnosis of cervical cancer because of examination of the cervix with the colposcope alone. It has, of course, been of inestimable value in showing the areas from which to take biopsies; it has been of great value in clarifying to the observer red spots, small duct openings, small cysts, and other changes in the vaginal epithelium that could not be recognized with the naked eye. Familiarity with the magnified cervix is extremely important and Hinselmann's colposcope, as used by most gynecologists magnifies the cervix ten times. There is no doubt but what early carcinoma can be diagnosed because of the colposcope but familiarity with the colposcope, even a large and long experience, does not necessarily make it possible to make an early diagnosis. It is necessary to take a biopsy from the suspected area and then the diagnosis is made on microscopic section. I have never found in my experience that it has been possible to say that I could not see the cancer with a naked eye, that it was visible only through the colposcope, and then after taking a biopsy find malignant disease. The colposcope is of great value in showing changes in the epithelium, cysts, open ducts, areas of roughening, and breaking of the mucous membrane.

*Schiller Test.* Based on the work of Lahm, Schiller (4) devised what he called the iodine test, best known as the "Schiller Test". This test is made by staining the cervix with a solution consisting of one part iodine, two parts potassium iodide, and 300 parts distilled water. This very light solution of iodine is poured into the vagina, allowed to remain three minutes and is then very carefully wiped out without rubbing the cervix. On inspection the healthy cervix which contains glycogen stains dark brown but areas of injury, areas of leukoplakia, or areas of cancer do not take the stain properly. Glycogen is present in the normal cervical epithelium which covers its entire external surface up to the external os. If there has been a laceration or an ulceration there will be no glycogen present and thus this area will not stain. Leukoplakic cells contain no iodine and also will not accept the iodine stain; carcinoma, having no glycogen, does not stain. Proper use of the Schiller solution and observation shows where a biopsy should be taken. The diagnosis will not necessarily be cancer but the epithelium will be abnormal or no epithelium will be present. The Schiller Test alone is not diagnostic. I have also used this test since 1933 and in no instance have I ever made a diagnosis of carcinoma of the cervix because of the use of the Schiller Test alone.

The combination of the colposcope and the Schiller Test is of great value,—the unstained areas can be carefully observed at considerable magnification, but this combination has not yet made a diagnosis of carcinoma of the cervix for me that I had not suspected previously. The colposcope and the Schiller Test are important in familiarizing the examiner with the typical appearance of normal and abnormal cervical epithelium.

*Biopsy.* After having used the vaginal smear, the colposcope, and the Schiller Test, the examiner should be ready to take a biopsy. The biopsy is not infallible. If the specimen removed contains carcinoma the Pathology Laboratory will report carcinoma. If the patient has carcinoma but the piece of tissue removed does not come from the area of the carcinoma the report will be negative; this sometimes gives a sense of false security. Therefore it is of importance in a patient who has a history of abnormal bleeding and who has a positive vaginal smear that various areas of the cervix be biopsied to make a proper examination of the cervix. A biopsy is best taken with a knife. The tissue should be of good size and thick and should be taken from the internal os out to the normal cervical epithelium. This is not possible in the office where, as a rule, punches of various sorts are used to remove pieces of tissue for diagnosis. It is not sufficient for a surgeon, gynecologist, or medical man to take a piece of the cervix in a patient with a suspicious history and feel that because the biopsy did not show cancer the patient has not a malignant growth. Pieces should be taken from various areas of the cervix and sent to the laboratory. Mistakes on biopsy are not great if the carcinoma is biopsied; if, however, it is not present mistakes may be very serious. Such mistakes are not laboratory errors but are due to the method of biopsy. Biopsy is of the ultimate importance but its weakness is due to the fact that the tissue removed may not be taken from a carcinomatous area. Many biopsies show no squamous epithelium at all and this is due to the fact that the biopsy was taken from an eroded area where there is only connective tissue and no epithelium. Therefore a biopsy of the cervix alone cannot be completely relied upon. It is much more satisfactory to have taken a vaginal smear, and to have done a colposcopic examination and the Schiller Test than it is to rely upon biopsy alone. When a piece of tissue is obtained from the cervix with a punch and it is found to be firmly adherent to the cervix and it takes a good deal of pulling and twisting to remove it the chances are that carcinoma is not present. Cancer is crumbly and friable and pieces of tissue break away extremely easily. This is most characteristic of malignant disease and the fact that it does break away easily practically always makes the diagnosis.

In patients suspected of endometrial carcinoma after the vaginal smear has been done the gynecologist is tempted to do an *endometrial* biopsy; this may be done with various types of small curettes and punches. Endometrial biopsies are of value in showing changes in the endometrium due to the menstrual cycle and are of value in the diagnosis of carcinoma only if it is positive. It is important in ruling out endometrial cancer that every part of the endometrial cavity be explored; if the specimen does not show carcinoma endometrial biopsy cannot be relied upon. Endometrial biopsies may come from two, three, or four, or as many areas as the operator wishes but it does not include the whole endometrium. A negative endometrial biopsy is of no value but a positive one, of definite value. It is necessary to advocate curettage if endometrial biopsy fails. Even with curettage it is extremely difficult to cover the whole cavity.

The ultimate method in diagnosis of carcinoma of the endometrium is that known as *curettage*, where with great care, under anesthesia, the whole uterine cavity is carefully explored. Many times a large curette is used and this, in the atrophied uterus, is not satisfactory. A small, sharp curette should be used which can penetrate to all sections of the endometrial cavity; such a curette is dangerous because of the possibility of perforating the small, soft uterus. The menopause uterus is tiny; it is very friable, and penetration is extremely easy and can occur without one's knowledge. Even a uterine sound passed into the cavity may easily penetrate it. Yet it is important to measure the depth of the menopause uterus before curettage can be safely carried out. A large curette cannot cover the cavity properly; a small, fine, sharp curette is essential. Such a curette can reach the cornu of the uterus on both sides because it is in that area and at the very top of the fundus that cancer can be missed.

*Frozen section* diagnosis of endometrial cancer is not at all satisfactory. Some pathologists are expert but mistakes are made. It is better to curette a patient, obtain material and send it to the laboratory, and then wait for the microscopic diagnosis. At the Pondville Hospital (Massachusetts Department of Public Health), and the Palmer Memorial Hospital we have adopted the plan of curetting the patient, making the diagnosis, and measuring the depth of the uterine cavity. A radium applicator of the proper length and size for application of radon is then selected and a radon needle made to fit. Relying upon frozen

section diagnosis in either cervical cancer or cancer of the endometrium is not safe. It is much better not to operate upon patients who have carcinoma of the endometrium, even if the frozen section should be positive, because radium should be given before surgery is done.

The early diagnosis of carcinoma of the cervix presents difficulties to the Pathology Laboratory. In frank cancer of the cervix or endometrium the diagnosis is easy. In patients with carcinoma of the cervix which is pre-invasive, or so-called "carcinoma in situ," the diagnosis can be extremely difficult. Te Linde (5) has shown that the diagnosis of "carcinoma in situ" may be misleading for in his cases after the uterus had been removed invasive cancer was nearly always found. These findings have been substantiated by our experience at the Pondville Hospital (Massachusetts Department of Public Health), where it was found that the diagnosis of "carcinoma in situ" refers only to that particular section, and in other parts of the cervix it may be infiltrating cancer. The proper treatment for pure "carcinoma in situ" is total hysterectomy but if the tumor is invasive it may be in the lymphatics and more radical surgery should be undertaken. The diagnosis of carcinoma in situ should not give the surgeon the feeling that the tumor is only skin deep; we must recognize the fact that in most instances this diagnosis means that infiltrating carcinoma is present.

## Conclusions

1. The early diagnosis of carcinoma of the cervix depends upon many factors.
2. We have more tests to work with than our predecessors had.
3. The vaginal smear is extremely important and grows in importance as technicians and pathologists become expert.
4. The colposcope of Hinselmann or the Schiller Test are valuable adjuncts.
5. Negative biopsy reports must be considered with great care.

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# Cancer Research in 1944*

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CANCER research, like all research, is difficult to correlate with any given time. Much of the work that appears in a given year has had its foundations laid years before, and sometimes work that appeared of very little account at the time proves to be of fundamental importance for major advances to come. Thus, the actual research that one can examine at a given time is much like the portion of an iceberg seen above water and the presence and character of the submerged nine-tenths is not appreciated.

There are three divisions of cancer research: work dealing with the causation of tumors, with the diagnosis of tumors, and finally with the therapy of tumors. One of the first items to be considered under the causation of tumors illustrates well how a concept of importance at the present may run back in rudimentary fashion for years. Emphasis is now being laid on the importance of somatic mutations as a possible starting point for cancer. This concept, of course, carries back to the work of Boveri, who in turn credits the idea to von Hansemann in the last century. Furth has pointed out that there are different transplantation patterns characteristic of different tumors, differing among themselves but each fairly constant. These might well be explained on the basis of somatic mutation. The frequency of mutations, particularly mutations induced by radiation, may be extremely high. This technique of using radiation-induced mutations has been of great importance to the plant geneticists in the recent years. Many useful types of grain have been evolved in part through induced mutations.

Of interest in any consideration of genetic aspect of tumors are the observations bearing on the alteration of these genetic factors, chiefly through the so-called milk factor of Bittner. The milk factor is familiar to us as a means of altering the susceptibility or resistance of mice to the development of mammary tumors. There is evidence accumulating that this may be extended to other types of tumors. The fundamental importance of some such substance, as yet unidentified but possibly related to the viruses, cannot help but attract the attention of research workers for a long period to come.

In the virus field there has been no appreciable change in the research pattern of the past few years. There exists a still-to-be reconciled divergence of opinion between those feeling viruses to be of primary importance in neoplasia and those, possibly equally correct, who relegate viruses to relatively minor importance.

Evidence has been accumulating to indicate that carcinogenesis induced by diverse agents may have fundamental properties in common, since sub-liminal doses of different carcinogens in themselves ineffective, when combined with one another induce development of a tumor. This was first suggested by the acceleration of induction of carcinoma produced by tarring the rabbit ear through inoculating the Shope papilloma virus. The synergistic effect has been observed in a wide range of agents, even the combination of chemical carcinogens and ultra-violet light.

The factors influencing the development of cancer in humans still elude us. However, there are some very suggestive leads such as the striking prevalence of cancer of the liver in Bantus, and yet the low incidence of primary cancer in the liver as seen in the American negro. This focusses attention on possible dietary or environmental factors. Racial differences in incidence of specific types of cancer are as yet queries to be answered. Steiner's studies on carcinogens in human liver are still to be completed. Through further study of multiple malignancy, additional evidence has been produced that there is an individual susceptibility to the development of cancer. 6% of Warren's series of cancer autopsies, now totalling 4000, showed multiple malignant tumors, approximately 11 times the expected incidence.

* Based on a talk presented at a joint meeting of the College of Physicians of Philadelphia, the Philadelphia County Medical Society, and the Philadelphia Division of the American Cancer Society at the College, April 25, 1945.

In the field of diagnosis the chief development has been in the application of research rather than in the development of new lines. The establishment of the prevention clinics, or perhaps better named, early detection clinics, is a step of significance, which may go far in reducing the mortality rate of malignant disease. Philadelphia is fortunate in having five of these clinics. The value of Dr. Macfarlane's clinic has influenced the International Cancer Research Foundation to expand the work and offer to the citizens of Philadelphia a greater facility for prompt and accurate diagnosis of malignant diseases than exists in any other locality. In relation to these cancer prevention clinics special diagnostic techniques have achieved prominence during the year. Papanicolaou's vaginal smear technique appears to be itself a reasonably effective method of screening large numbers of women and selecting those needing special study of the genital tract.

The concept that certain groups of the population possess a special risk of developing cancer deserves further emphasis. Thus, it has been demonstrated that the woman with chronic mastitis has a greater chance of developing cancer of the breast than the normal woman, or that the individual with keratotic skin has a greater chance of developing skin cancer. Hence, the follow-up in these special groups should be checked with particular care.

One point of fundamental importance to the prevention or detection clinic yet to be decided is the marginal utility of such agencies. When one considers that in the faithful work of Dr. Macfarlane and her group (10,325 examinations over a period of years) only 10 cancers were found; when one considers the painstaking roentgen examinations of the stomach made at the Presbyterian Hospital by Swenson and his associates of 2413 cases to find 3 malignant tumors, it leads one to wonder whether the cost justifies the results. This is a matter that time alone can tell. Perhaps in a world hardened to the slaughter of millions we may have come to set too low a cash value on an individual life.

What the diagnostic significance of the presence of fluorescence due to porphyrins in secretions may have is yet to be determined. Similarly the practical value of the striking observation of Green that heterologous malignant tumors will readily grow in the anterior chamber of the eye of the rabbit or guinea pig, whereas heterologous normal tissues or benign tissues will not grow has yet to be determined.

In the field of therapy no striking advances have been made. Rather there has been a further sifting of therapeutic measures, a growing and healthy discontent with some of the present methods of therapy. The hormonal field has occupied the attention of a number of research workers. Orchidectomy with or without the administration of stilbestrol, or stilbestrol alone has achieved striking remissions in prostatic cancer, and strangely enough in a few cases of cancer of the male breast. Among experiments those of Lipschütz are of interest, bearing on the induction of fibroid tumors in the guinea pig by estrogens and the counteracting effect of the steroid hormones. Also of interest are the observations of Murphy and Sturm on the effect of steroids on the lymphoid apparatus and in experimental lymphoid leukemia. These latter points are highly suggestive, but what their applicability may be has yet to be determined.

In the field of radiation the war has enormously advanced the development of super-voltage machines. What, if any, advantage these may have for therapy has yet to be proved. Our experience with the radium pack is not such as to encourage too sanguine expectations from X-rays generated even at tremendous voltages. The radioactive isotopes have, of course, occupied a major place in therapeutic research in recent years, just as their use as tracers has been of major importance in all fields of research. The cyclotron has opened an enormous field for us in the isotopes. Phosphorus is the only radioactive isotopes that has in any way been actively explored. Radioactive sodium may well in post-war years displace radium. Thus far it is apparent that it is not enough to get radioactive material into the tissues. One must have that radioactive material in sufficiently heavy concentration on the one hand, and the tumor cells must be sufficiently susceptible on the other hand to achieve an adequate result. Thus it is possible to deposit radioactive strontium highly selectively in an osteogenic carcinoma, but once deposited there it is without significant effect owing to the resistance of those tumor cells to radiation.

Finally, a word with regard to specific chemotherapeusis. There is not any specific chemotherapeutic agent potent against cancer. However, we would be blind to close our eyes to the

possibility that some day there may be found some potent substance among the great range of compounds, organic or inorganic, now known or to be known. We do know that orthocresyl phosphate, known through the Jamaica ginger paralyses, has a specific effect on the anterior horn cells of the spinal cord. We know through the brilliant experiments of Shaw Dunn that alloxan will specifically pick out the beta cells of the islands of Langerhans and destroy them in a concentration that is relatively harmless to other cells of the body. Out of a vast number of substances tried we have two highly specific chemical agents. It is not impossible to hope with further large scale testing we may turn out other substances that may be specific not only for a cell type, but possibly for a malignant variant of the cell type.

In any survey such as this one cannot help but wonder what bit of research at present almost unheeded may actually be the basis of some major accomplishment years to come, just as Lord Rutherford's hint in 1920 and Bothe and Becker's later combination of polonium and beryllium led ultimately to the development of the cyclotron, the radioactive isotopes and the actual transmutation of elements.

Any consideration of cancer research at the present time would be incomplete were one not to consider the very significant move made toward more adequate support of the total research program. The drive this month sponsored by the American Cancer Society has potentialities for a vast deal of good. The acceptance by the community of cancer research as a definite responsibility is a step that will go far in advancing our knowledge and reducing the morbidity and mortality from cancer.

# A Note on the Placebo

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IT IS interesting that apparently there has never been a paper published discussing the important subject of the placebo. This is evidenced by the absence of this topic from the Index of the Surgeon General's Library and from the Cumulative Index. No doubt this valuable item of our therapeutic armamentarium is mentioned repeatedly in articles under other headings but it deserves at least one reference all its own. Every one of us has often used the word and often prescribed the placebo, yet how many of us realize how little has been written and how little is known of the history of this word and this type of treatment. It receives not one mention in La Wall's delightful "Two Thousand Years of Pharmacy".

The word itself, of course, is the first person singular of the future indicative of the latin verb "to please", so it would seem to be an excellent name for a drug given for its psychotherapeutic effect and having no pharmacologic action whatever. Let us now look the word up in the Oxford "New English Dictionary"—as so often happens we find more than we knew.

The first use given for the word placebo is as the name commonly given to Vespers in the Office for the Dead in the Latin service. This use dates back at least to the 13th century and in 1380 Wyclif writes "Prelatis ben more bounden to this prechynge . . . than to seie matynes, masse, evensong or placebo". At this service in the Roman Church a part of the CXVI Psalm is recited in Latin—"Placebo Domino in regione vivorum" which it would seem should be translated "I will please the Lord in the land of the living" but which in both English prayer book and King James Version reads "I will walk before the Lord in the land of the living". This variation stems back to the use of the Hebrew verb "halak" (pronounced hawloch) which means "to walk habitually" and occurs constantly in such phrases as "he walked before God", hence was pleasing to God. Our little research has led us deep into ecclesiastical matters.

Continuing in the dictionary we find the second use of placebo to be in allusive phrases such as "to sing a placebo" or "to be at the school of placebo" meaning to play the sycophant or to be servile. This also is an old use of the word for in Chaucer we find the sentence "Flatereres been the deueles Chapelleyns that syngen euere Placebo". Number three of the uses of the word finds it a noun meaning a flatterer, sycophant or parasite and again in Chaucer a character of this type is given Placebo as a proper name.

It is not until heading number four, that we come to its use as "an epithet given to any medicine adopted more to please than to benefit the patient". This is quoted from Hooper's Medical Dictionary which is the earliest use of the word in this way recorded in the big Oxford New English Dictionary which always records a word's first known use in literature. This edition of Hooper's Dictionary was not published until 1811, at least five hundred years after the word was used in other manners. It is interesting to speculate on this tardy appearance of placebo in medical terminology and to search further. One might expect to find this use far earlier. At first thought, one might anticipate it to be very old and probably the use of medicines in this fashion is as old as medicine itself; but remember that in olden days the physician had no method of distinguishing the drugs which had true actions from those wholly inert. All were considered powerful, none truly were; it would have been iconoclastic to doubt any. So perhaps in the times before the Countess of Chinchon in 1638 there was no basis for terming anything a placebo. This supposition is supported by finding the word in the 1787 edition of Quincy's Lexicon defined as "a commonplace method of medicine" which in one sense is only too true. With this same definition it also appears in the Philadelphia Medical Dictionary published in 1808 by John Redman Coxe.

This wise definition—a commonplace method of medicine—may illustrate the earliest stage of doubt concerning the efficacy of the weird prescriptions of those days and an approach to the frank admission of a quarter of a century later

that one might wish to give a placebo—to please without benefit.

In the 19th and beginning of the 20th centuries the placebo was freely prescribed and the word was in daily use. Nevertheless it is amazing not to find the word placebo in the index of H. C. Wood's famous Therapeutics whose 14 editions covered the period from 1875 to 1908. If Wood was unwilling to discuss placeboes it is not surprising to find that the modern books on treatment—Barr, Beckman, Clendening—turn up their more scientific noses at this humble humbug. The giving of a placebo—when, how, what,—seems to be a function of the physician which, like certain of the functions of the body, is not to be mentioned in polite society. Yet there is a certain amount of skill in the choice and administration of a placebo. In the first place, it must be nothing more than what the name implies—a medicine without any pharmacologic action whatever. Even a mild sedative is not a true placebo. Secondly, its name must be unknown to even the most inveterate patient who knows most drugs by name and is always quick to read the prescription. If the medicines named are familiar the type of patient who needs a placebo will promptly exclaim that this or that drug had been tried and "had not helped me" or "had upset my stomach". It is well if the drug have a Latin and polysyllabic name; it is wise if it be prescribed with some assurance and emphasis for psychotherapeutic effect. The older physicians each had his favorite placeboic prescriptions—one chose Tincture of Conderango, another the Fluid extract of Cimicifuga nigra. Certainly this latter by its Latin name might be expected to have more supratentorial action than if one merely wrote for the Black Cohosh, and Conderango would be more efficacious than sugar of milk.

But is there any need or excuse for ever giving a placebo? What, in other words, are the indications? Often the physician is forced to prescribe some medicine for a patient before any diagnosis has been reached. This is especially true when the patient is ignorant and does not understand that diagnosis must precede intelligent treatment. Sometimes there is no indication even for symptomatic treatment and yet the patient will be disappointed and displeased if no prescription is given even at the very first visit. Again, there may be a time when during the carrying out of diagnostic tests it is undesirable to give any potent medicine lest it interfere with the tests and yet the patient must be encouraged by treatment. None of this perhaps is necessary if the patient and family are sufficiently intelligent—but unfortunately few are.

In the hopeless, incurable case the use of a placebo will often postpone the use of sedatives or will lessen the quantity that must be given even if there is pain. The human mind is still open to suggestion, even in these modern and disillusioned days. The sympathetic physician will want to use every help for these pathetic patients and if the placebo can help, he will not neglect it. It cannot harm and may comfort and avoid the too quick exhaustion of opiate efficacy. The placebo is part of what used to be called the art of medicine—that discredited sister of scientific medicine. There is still a good deal to be said for the art of medicine and always will be and when our final illness comes let us hope that before the Placebo is pronounced over our remains we shall have been under the care of a physician not too scientific and yet not a placebo, who will not hesitate to smooth our path even by the use of a well prescribed placebo.

# Let Us Look Over the Collections of the College of Physicians

*By* ELLA N. WADE

*Curator of the Mütter Museum and Custodian of the College Collections, College of Physicians of Philadelphia*

THE famous collections of the Mütter Museum are not the only ones to be found in the College of Physicians. Scattered throughout the building are many objects of artistic, historic and scientific interest known as the College Collections. Among these are the oil portraits that decorate the walls, the framed photographs, engravings, etchings, prints and historic documents that we sometimes think clutter them, pieces of statuary, medical medals and badges, and a variety of miscellaneous memorabilia, some of sentimental value and others so rare as to be priceless. In this collection we also find material which seems to belong rightly in the collections of the Museum, but which the donors hesitated to place there where it would be held permanently within the confines of the Museum, bound by Doctor Mütter's Deed of Gift, never to be loaned or used outside of the building.

There are 111 oil portraits, the majority of the subjects having been distinguished Fellows of the College of Physicians. Many of them were painted by the country's most noted contemporary artists. There are portraits of Dr. S. Weir Mitchell and Dr. William W. Keen by Robert W. Vonnoh; Dr. Nathaniel Chapman and Dr. Thomas Tickell Hewson by Thomas Sully; Dr. Arthur V. Meigs by William M. Chase, and Dr. William Thomson by Thomas Eakins. These are but a few of the very excellent paintings of prominent physicians done by artists as equally renowned in the field of art. These likenesses of the great men of former generations look down from the walls of the lecture rooms and hallways of the College, giving mute encouragement, and inspiring the present and future generations of the medical profession to new heights of scientific achievement.

We do not know who painted many of our very early portraits, for no signatures appear on the canvases. If they once did, time has erased them. This is to be regretted, as is also the fact that donors did not, at the time of presentation, accompany each portrait with proof of its authenticity. If this were done it would spare the College considerable embarrassment, and eliminate what, unfortunately, often proves to be vain efforts to trace them. Several times we have removed legends that had been attached to portraits for many years, because art critics were convinced that the subject or the artist was erroneously named. Having no record, either in the minutes of the Committee on College Collections or in the minutes of the Council of the College to give proof, we accepted the opinion of the experts and removed the labels. As their true identity has never been established such pictures stand in our catalogue as nameless or doubtful.

Not long ago we were the recipient of such a painting. It was presented as the portrait of Dr. Benjamin Rush by Benjamin West, but no proof that it was authentic accompanied it, and the officers of the College were unable to obtain any convincing evidence from the donor. Experts were invited to inspect the painting. They were of the opinion that it was not a picture of Benjamin Rush and also that it had not been done by Benjamin West. A Fellow of the College, however, who makes a study of works of art and does considerable research along that line, for definite reasons feels certain that the portrait *is* authentic, although he can furnish no positive proof. Therefore, this picture, although it occupies a conspicuous place in the reception hall of the College where it adds materially to the adornment of that lovely room, must appear in the catalogue as a "portrait of an unknown man by an unknown artist," or "portrait supposed to be Dr. Benjamin Rush, supposedly painted by Benjamin West."

An amusing incident in connection with this portrait occurred recently when an old gentleman, who claimed to be an authority on art, came into the Museum to inquire about it. He, himself, did not think it was a picture of Benjamin Rush

by West, but felt quite sure that he could trace its identity. We regret to state that any hope we momentarily entertained that the gentleman might help us, was quickly dispelled when it was learned that he considered himself to be a "psychic", and more frequently than not, received his information from the spirit world. Needless to say the discussion was terminated as quickly but as politely as possible, for with all due respect to his earnest belief in the subject, it seemed hardly probable that the dignified members of the Committee on College Collections would accept the opinion of some ghostly expert, even though legitimate channels had failed to produce results.

Invariably in a collection of portraits, although there may be many which are true works of art, and others that we are told are excellent likenesses of the subject, there are one or two that have some special appeal. This seems true of the portrait of Dr. Jacob DaSilva Solis-Cohen which hangs in Thomson Hall. I do not know how this ranks with those paintings that are considered our best by art connoisseurs, or what monetary value would be placed upon it, but it has always seemed to be more than just a face on a canvas. It is a small picture of a thoughtful old man, who seems to have come almost to the end of a long and weary road. Although he was the pioneer Laryngologist in America, of world wide reputation, and author of the first book on Laryngology ever published anywhere, in this portrait he might be anybody's beloved, tired old grandfather. This painting of a former Fellow of the College of Physicians, and former Honorary Professor of Laryngology at the Jefferson Medical College, was done by Mr. W. T. Thomson simply because of the interest of the artist in his subject, and came to us quite by accident. It was done in the last year of Dr. Solis-Cohen's life, and remained in Mr. Thomson's studio for twelve years thereafter until seen by Dr. E. J. G. Beardsley, a Fellow of the College, who attended the artist during an illness. Doctor Beardsley immediately contacted Dr. George Morrison Coates, thinking someone interested in Dr. Solis-Cohen might like to purchase it. After Doctor Coates had seen it he took the matter up with the Executive Committee of the Section on Otolaryngology, and was authorized to collect, by subscription, the money with which to purchase it. It was presented to the College January 16, 1939 by the Section on Otolaryngology.

The hanging of a newly presented portrait is often a trying task for the Committee whose business it is to find a suitable place for it, because while the members endeavor to respect the wishes of the donor as to location, they are seriously hampered by lack of wall space. In Mitchell Hall, where the majority of the portraits are of former Founders or past Presidents of the College, it is a relatively simple matter, and the portraits are hung so as to form a certain symmetry. Panels at the back of the hall are perfectly adapted to single portraits, and they are as conspicuous as any others in the room. But in the smaller halls, where are hung the portraits of physicians active, or at one time active, in the societies which hold their meetings there, a delicate problem presents itself. Perhaps the Committee has seen fit, because of the size of a canvas and the style of the frame, to hang the portrait of Dr. X—— on a side wall toward the front of the lecture hall. To friends of Dr. Y—— this space may seem a prominent one where the portrait of Dr. Y—— should hang. Suggested changes are made frequently if it is at all possible, but still there always seems to be some picture, which in someone's opinion, should be somewhere else.

The small framed photographs, etchings, engravings, documents, etcetera, were probably of interest at some time to someone. It is supposed that the majority of them still are, but there are 465 in the collection, and for various reasons they often seem to be a nuisance, although one cannot belittle their historical importance. There are 120 of these pictures in the Norris Room, and 67 of them in the Clerk's office, where they dance around nimbly on their hooks to the tune of rumbling traffic, coming to rest at last, at all angles. They are straightened periodically, but the vibration eventually moves them again, sometimes only a fraction of an inch, but even that is enough to make them look crazily awry, and nothing we do seems to remedy it. Cleaning them alone is a task that takes many hours, and often when this is done we discover that many need new backs, or a picture must be taken from its frame so that the inside of the glass may be cleaned and accumulated dust removed. All must be handled gently, for the paper is brittle because of age, and very easily damaged.

There are fine engravings and etchings of famous individuals and historic scenes, but many pictures of men and scenes are unidentified. We have no record of the donors, and they are so old that anyone who might have been able to identify them has long since passed on. Their

only identity is a catalogue number, which gives the rather ambiguous information, "Photograph of a man (?)," or "Etching of a scene (?)."

Still others are of no medical interest. For instance, there is an engraving of the Girard Trust Company in the Clerk's office, and also a small picture of a horse's head. Our catalogue tells us this latter was the last fire horse in Philadelphia, but as it was presented in 1879 we know it to be an error, for there was no mechanized fire apparatus at that time. It may have been the *first* fire horse in Philadelphia, but even so, why should it or the picture of the Girard Trust Company be displayed in the College of Physicians? Perhaps some reader may know the answer to this, and there may be some logical reason why they are exhibited, but so far we have been unable to discover it. The reason for showing two small pictures which hang behind the door on the lower floor of the Mütter Museum is sometimes questioned. One is of a group of Chinese *before* beheading, and the other of a group of Chinese *after* beheading. Since we do not know why these Orientals were beheaded, the photographs merely picture a gruesome end to a few individuals, who, whether they deserved such a fate or not, certainly do not contribute anything to medicine by being shown with and without heads.

Because there are so many of these small pictures so widely scattered throughout the building, it is impossible to know at a glance what each represents or where certain ones may be located without consulting the catalogue. It seems hard for people to realize this, for occasionally someone is quite upset if we cannot tell him immediately where to find the small crayon of his grandfather, although he tells us it was "presented to the College in 1892," and "is about so big."

The statuary in the College consists of bronze, marble and plaster busts of eminent physicians. One of the finest of these is the marble one of Dr. S. Weir Mitchell which occupies a marble pedestal in Mitchell Hall.

On the first landing at the head of the broad marble staircase stands the full length statue of Aesculapius, a replica of the one in the Vatican, which was generously donated by Dr. Richard H. Harte. The busts occupy various niches and pedestals in different rooms and hallways of the College building.

The most recent acquisitions are the bronzed plaster bust of Prof. Wilhelm Konrad Roentgen by Christabel Cummings, presented by Dr. George E. Pfahler, and plaster busts of Dr. William W. Keen, Dr. Henry Beates and Dr. James Cornelius Wilson by Samuel Murray, given to the College by the sculptor's widow, Mrs. Jane Murray, through our good friend Dr. William N. Bradley. The one of Doctor Keen has a bronze finish and is an excellent one.

The collection of medical medals and badges is a fairly new one, for in 1926 it contained but 37 pieces. Although it is still small compared to a collection such as the one in the Army Medical Museum in Washington, it has grown until it now numbers 321 pieces, many of which are rare and valuable.*

It is sometimes difficult for the members of the Committee on College Collections to decide whether a donation warrants a recommendation of its acceptance by Council, or whether it should be returned to the donor as unsuitable. Some very unusual items sometimes arrive for the Collection. Relatives of some deceased physician with the very best of intentions, gather together everything that appears to be medical that was left by the man, and dump them into the lap of the College. Usually everything received is well worth while, but occasionally something arrives that no one can name, no one has ever seen, and visiting physicians cannot identify. Among a collection of instruments, one time, appeared an ornamental silver ring about two inches in diameter. Thinking of it as a medical instrument, since it came in such a collection, it was tentatively identified as a weight, a pessary or a replica of some ancient medical apparatus, but it was Doctor Batson who solved the puzzle when he told us it was a handle from some loving cup.

A donor almost always has a plausible reason why his gift would be a valuable addition to the collection, but the Committee is always kindly disposed toward that donor who relies on the discretion of the Committee. Then, in the event that the article is a duplicate or of little interest, the Committee knows it may decline to recommend its acceptance, or relegate it to the storeroom for some future use without offending the person or persons who gave it.

The miscellaneous section of the College Col-

* For a description and catalogue of the medals, see Mrs. Wade's "Medical Medals in the Collection of the College of Physicians of Philadelphia", *Bull. Med. Lib. Assoc.*, 32:177–213, April, 1944. [Ed.]

LIBRARY OF THE
COLLEGE OF PHYSICIANS
OF PHILADELPHIA

lections contains many instruments personally used by distinguished physicians, and personal belongings of eminent doctors, such as canes, ash-trays, match-boxes and timepieces. In the collection is the silver trowel used by Dr. S. Weir Mitchell on the occasion of the laying of the corner stone of the present building of the College in 1908, and a piece of polished foundation stone from the old building of the College at the northeast corner of 13th and Locust Streets. The collection also boasts of a number of unique seventeenth century Singhalese physicians' daggers and styli which were used respectively for cutting the leaves of the Talipot palm to make the Ola, and writing upon the Ola. The Ola, from Kandy, Ceylon, dating back to 1650 A.D., was presented by Dr. Casey Wood in 1925. The manuscript is written in Singhalese and consists of favorite prescriptions, some of them in verse, for children's diseases. There are many other interesting exhibits in this collection, but chief among them are the contents of the Abbe Case, known as the Abbe Collection.

About 1919 Dr. Robert W. Abbe of New York, an associate Fellow of the College of Physicians of Philadelphia, with the presentation of the gold watch of Dr. Benjamin Rush, started what he desired to be a rare collection of mementos of great and historical medical figures, who have added much to the advancement of medical science. Adequate funds for purchasing a cabinet and for increasing and maintaining its contents were also provided by Doctor Abbe.

The Abbe Cabinet stands in Ashhurst Hall where its many treasures may be viewed by visitors or regular readers in the library.

In addition to Dr. Benjamin Rush's watch, which is said to be a perfect timekeeper still, we are in possession of one of his silver shoe buckles set with brilliants, presented by his granddaughter, Mrs. J. Biddle Porter. A small oil miniature and silhouette of Doctor Rush, presented by Dr. George Muller a few years ago, also occupies a place in the Cabinet.

The mementos of Dr. Edward Jenner consist of an inkstand and a lock of his hair. The inkstand was the second memento to become a part of the Abbe Collection. It consists of three glass wells in a silver tray. It came into possession of Dr. S. Weir Mitchell, who himself used it and at his death presented it to the College of Physicians. Even so distinguished a gentleman as Doctor Mitchell must have experienced a thrill as he dipped his pen into a well that had received the quill of the discoverer of vaccination. The lock of hair of Edward Jenner was contributed by Sir William Osler.

Part of Lord Lister's equipment while developing his principles of antiseptic surgery in Glasgow, Edinburgh and London was a small case of surgical instruments. These instruments, with the owner's name engraved on the cover of the case, and also the original tubes for tests of lactic acid and fermentation, came to the College through Sir Rickman Godlee, whose wife was a niece of Lord Lister. Worthy of sharing honors with these mementos is the carbolic spray apparatus which Lord Lister used in his clinic, and which was presented by Dr. W. W. Keen who received it from the noted surgeon himself.

From Pasteur we have the model of a tartrate crystal which he made, labelled, and mounted to demonstrate the nature of crystals from wine fermentation.

Mme. Marie Curie presented the instrument which is known as the "quartz-piezo-electric" apparatus, used to determine the strength of electrons discharged from radium and also illustrates the fact that crystalline substances, when compressed or expanded, emit electrons, due to the strain put upon them. In the instrument there is a long piece of quartz crystal held by one end and weighted at the other. The electroscope, placed opposite the face of the crystal records the discharge of electrons, in exact proportion to the weight put upon it.

A letter from Mme. Curie to Doctor Abbe at the time of the presentation March 1, 1921, reads as follows:

"Dr. Robert Abbe

Dear Sir,

It gives me pleasure to present this apparel "quartz piezo electrique," for such purpose as its historical interest will serve. It was designed by Prof Curie and is one of those used by us in our early research work for measuring the radioactivity of Radium Having served its purpose it was replaced by other apparatus.

M. Curie."

Several morocco bound volumes containing letters and signatures of Rush, Jenner, Lister, Pasteur and Curie, and various printed, typed and hand-written data and clippings applying to these scientists appear with other exhibits.

The most recent memento to become a part of this collection is a small silver urn which formerly belonged to Dr. S. Weir Mitchell. Such receptacles were used to hold locks of hair or other personal souvenirs. It was presented to Dr. Francis R. Packard in 1945 by the widow of Dr. John K. Mitchell, son of Dr. S. Weir Mitchell. Before giving it to Doctor Packard, Mrs. Mitchell had Doctor Packard's name engraved upon it, where the names of its five previous owners appear. It had belonged successively to Drs. Anthony Fothergill, Joseph Parrish, George B. Wood, Horatio C. Wood, and S. Weir Mitchell.

The Abbe Cabinet now contains as many objects as it can conveniently accommodate. A new case will be necessary before many new additions are made to it since those already displayed are somewhat crowded.

Nearly every month brings some new gift to be added to the less rare collections of the College. Recent acquisitions have been a number of interesting medals and several ophthalmoscopes, the types of which were not previously in the collection.

Because we already have so many small framed pictures and documents and little space in which to hang more, new donations of this sort usually are taken from the frames at the time of presentation and given to Dr. Samuel B. Sturgis for what is known as the "Sturgis Collection." This does not come under the jurisdiction of the Committee on College Collections, but it is a collection in which everyone familiar with the College and its activities will be interested. The pictures and other papers are beautifully mounted in large portfolios where they are better preserved than when hanging on a wall where they fade and collect the dust of years. Eventually these portfolios will be given a special place in the building, where, after being catalogued, they will be available to anyone who wishes to see them.

While interest in the Mütter Museum may be gauged by the number of daily visitors, we are unable to judge how many who come into the building are interested in the College Collections. One cannot be unaware of this collection, for no matter into what part of the building one may go, he is sure to see part of it.

It is true that little impression is made by those things which are always in their accustomed places, and they are apt to be seen as a part of the furnishings rather than part of a collection. It is thought with special attention called to them, visitors to the building may become conscious of them as objects of art and exhibits of scientific and historic interest in the Collections of the College of Physicians.

# Memoir of Arthur A. Stevens

*By* TRUMAN G. SCHNABEL

ARTHUR A. STEVENS, Fellow of the College for forty-three years, died at his home, as day was dawning on June 10, 1944. He continued to the end a solicitous, understanding and skillful doctor. After expressing deep regret to a colleague for the need of being called so early on that June morning, he went on and said with great difficulty, that he was having an attack of acute pulmonary edema, numerous premature contractions resulting from another coronary occlusion and that the end was near at hand.

It was in this same home that he had lived, practiced medicine and wrote medical text books for forty-six years. His many patients and hundreds of medical students, who took his private quizz in medicine, will long remember his simple and unpretentious offices. In the small desk located in one corner of his consultation room, there were found, after his death, two slips of paper, on one he had written Osler's "The knowledge which a man can use is the only real knowledge, the only knowledge which has life and growth in it and converts itself into practical power. The rest hangs like dust about the brain and dries like rain drops off the stones." On the other, were written Huxley's "Let us sit down before fact as a little child, be prepared to give up every preconceived notion and to follow humbly where-ever nature leads". These quotations were obviously highly treasured and must have stimulated and sustained him scientifically and intellectually for most of his life. Likewise, shedding some light on his philosophy of practice, are the sublime lines of Tennyson's "Ulysses":

"Yet all experience is an arch where thro'
Gleams that untravell'd world, whose margin fades
Forever and forever when I move."

Save for the first three words "Yet all experience", Doctor Stevens used this last quotation on the title page of his "Manual of the Practice of Medicine". It is interesting to note too, that he margined these same lines with lead pencil in his beautiful, but now well worn volume of Tennyson, which he won as a prize at the age of fourteen in declamatory competition.

Arthur Stevens was born in Germantown, the son of Benjamin Stevens and his second wife, Susan Widdis. His father had migrated from Nottingham, England, at an early age and later in life manufactured knitting machines. His mother came of a mixed lineage, was sturdy, forceful and exerted a salutary influence on her large family. Samuel Longfellow, a Unitarian clergyman and a poet, like his brother Henry Wadsworth, lived near by on the Watson Estate and left a lasting impression on young Stevens, by chatting with him each day en route to school. Near by too, was a certain Major Ent, maker of drums, whose shop and personality were also a source of unending interest to "Reds" as his boyhood friends nick-named him. Besides these, there was his oldest sister, an able school teacher, who was always ready to help and encourage him and probably influenced him in the choice of medicine as his life's work.

Our late Fellow attended Public School, the Boy's Combined School, received his Bachelor's degree from the old Central High School on North Broad Street and his Master's degree from the same institution several years after his undergraduate days in Medicine at the University of Pennsylvania. His secondary school teachers always remembered him as a brilliant, spirited pupil, possessed of his mother's keen sense of humor and, of course, his well known ocular twinkle. He was not athletic.

He continued in Medical School at a high scholastic level and while studying, was an active member of a Quizz Club whose membership consisted of a limited number of his classmates. In spite of the legality of so doing, he was granted his degree in Medicine on May 1st 1886, two days before he reached his twenty-first birthday. On advice of Dean Tyson, he took the voluntary fourth year course which was then offered in anticipation of the four year course of medicine instituted some years later. After the extra year, which proved to be highly profitable, under the personal instruction of ranking members of the faculty, he passed with Osler through "Old Blockley's" postern gate for his year of internship.

Osler had arrived in Philadelphia in the fall of

1884 and so it was that the youthful Stevens "sat at his feet" for four of the five years which the Canadian spent in Philadelphia. Some thirty or more years later he dedicated his "Practice of Medicine" to "The memory of Sir William Osler, medical philosopher, master clinician and trusted counselor". After his interne days at the "Philadelphia Hospital" his "trusted counselor" advised him to go abroad for study and then the record shows that Doctor Stevens devoted a year to postgraduate work in Vienna and London. Back again in Philadelphia, in 1890, he was then well equipped for any medical opportunity which might present itself.

Several years thereafter he married Sarah McNabb who shared with her husband the love of good books, music, the stage and the arts generally and for a number of years was his traveling companion on trips to Europe and elsewhere. She was invalided for some years before her death in 1933, when she had the tender and loving care of her physician husband.

Extra mural quizzes being a part of the pedagogic program of that day, having an alert retentive mind and with his material well in hand, he became a natural for quizz mastership. Some years later he assumed responsible teaching assignments in the intra mural curricula of his Alma Mater, as well as that of the Woman's Medical College. In one or other institution, at some time, over a number of years, such subjects as physical diagnosis, medical terminology, pathology, therapeutics and clinical medicine came within the purview of his teaching. It has been said that he was a natural quizzmaster, but he did well too in formal bedside and clinic teaching. Here he made good use of the question and answer technique to drive home the catalogued details of his picture, he made skillful use of analogy and held the attention of his students with an animated, pithy, almost eloquent delivery. He had participated in amateur dramatics at one time and frequently gave Shakespeare with the skill of a professional at the request of fellow members of his Quizz Club, fellow internes and friends. The benches were well filled for his hour as evidence of his undergraduate popularity. His students were agreed that he was a most helpful teacher, one of the "old school", not too thought provoking, but of a drilling and compelling type. He really liked to teach and probably derived much personal satisfaction and pleasure out of his pedagogic life.

It must be noted here, that he derived an equal degree or perhaps a greater amount of satisfaction from his literary efforts. Reference has been made to his "Manual of Practice", first published in 1892 and to his large volumed "Practice" which appeared some thirty years later. When Doctor Stevens went to London in 1889 he carried with him a card of introduction from Osler to the celebrated Lauder Brunton, subsequently Sir Thomas Lauder. At the time, Brunton was an assistant physician to St. Bartholomew's and maintained his own pharmacological laboratories in the same institution. He was particularly interested in the "application of the physiological findings of pharmacology to internal medicine". This contact was a mutually happy one and probably stimulated the young American to write, after his home coming, a "Manual of Therapeutics" which included in subsequent editions Materia Medica and finally became a real "Textbook of Therapeutics". His list of published books also includes a "Textbook of Medical Diseases for Nurses", written in collaboration with Florence Ambler. The text of this work has been translated into Chinese. It should be added that at least eleven medical magazine articles appear in his bibliography.

His books were written in a clear, simple, forceful style. The manuals were, of course, boiled down to essentials and were very useful to medical students in preparation for examinations. His works, covering materia medica and therapeutics, were convenient and useful reference volumes for students and practicing physicians. His large "Practice of Medicine" was his best achievement. It compared very favorably with similar texts of that day and was, of course, done single handed. Whatever one wishes to say about the Stevens group of books, and discounting skillful publisher salesmanship, the fact remains that they ran through a total of thirty-five editions and approximately two hundred and seventy-one thousand copies, which is tribute enough to any authorship.

Doctor Stevens has been characterized in divers ways by students, colleagues, patients and friends. Some recognized a certain buoyancy, a quick step, a friendly smile, a sparkle; some a dynamic forcefulness and spirituality, but always the unfailing qualities of a gentleman. Others recognized a certain shyness, especially in the face of a large company, but not so in small groups, a becoming modesty and simplicity of taste. Certain it is, that he was generous to a fault in others, understanding and guileless. His day

was a punctilious one and always included time set aside for reading the Bible. He was likewise a great student of the "Bard of Avon". His copies of Shakespeare were worn out at the time of his death. Your memoirist will never forget the occasion after a small dinner party, when at the behest of his old friend B. Franklin Stahl, Doctor Stevens did the graveyard scene from Hamlet, much to the great delight and complete satisfaction of those present.

He was at one time physician to the Philadelphia General, Episcopal and St. Agnes' Hospitals. He loved "Old Blockley". Writing books is a big, time consuming job, especially when new editions must be kept abreast the times; adding thereto his teaching load, private patient and consulting practice and we have enough to make for more than a full life. It can then be said that Arthur Albert Stevens wrote his life well and spent it well, two circumstances as Carlyle wrote "equally rare in the lives of men."

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*1865:* May 3rd, Born at 5220 Greene Street, Germantown, Phila., Pa.

*1879:* Graduated, Boys Combined School, Germantown, Phila., Pa.

*1883:* A.B., Central High School, Phila., Pa.

*1886:* M.D., University of Pennsylvania Medical School, Phila., Pa.

*1887–1888:* Resident Physician, Philadelphia General Hospital.

*1889:* Post Graduate student, Vienna and London.

*1889:* Honorary Membership, D. Hayes Agnew Surgical Society, U. of P.

*1893:* June 27, Married Sarah McNabb.

*1887–1921:* Instructor and Lecturer on Physical Diagnosis, Medical Terminology and Medicine, University of Pennsylvania Medical School, Phila., Pa.

*1922–1931:* Professor of Applied Therapeutics, U. of P. Med. Sch., Phila., Pa.

*1893–1897:* Demonstrator of Pathology, Woman's Medical College, Phila., Pa.

*1895–1904,* Curator of the Museum, Woman's Medical College, Phila., Pa.

*1898–1906:* Professor of Pathology, Woman's Medical College, Phila., Pa.

*1906–1923:* Professor of Materia Medica, Therapeutics and Clinical Medicine, Woman's Medical College, Phila., Pa.

*1906–1914:* Assistant Physician, Philadelphia General Hospital.

*1914–1933:* Chief Medical Service, Philadelphia General Hospital.

*1893–1919:* Chief Medical Service, St. Agnes' Hospital, Phila., Pa.

*1919–1944:* Consultant Physician, St. Agnes' Hospital, Phila., Pa.

*1900–1920:* Physician, Medical Board, Episcopal Hospital, Phila., Pa.

*1898:* Member, American Medical Association.

*1898:* Member, County Medical Society of Philadelphia.

*1901:* Fellow, College of Physicians of Philadelphia.

*1944:* June 10, died.

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# Random Notes by the Librarian

*Those who cannot remember the past*
*are condemned to repeat it—*
*G. Santayana*

## I

*The Forthcoming Exhibit of Medical Illustration*

"Skilled Hands of Medical Artists Bring Macabre Beauty to Science" is *Newsweek's* slightly macabre heading for its article (April 2, 1945) describing a remarkable exhibit of contemporary medical illustration now touring the country under the aegis of the magazine *Modern Medicine.* The exhibit is scheduled to play its Philadelphia stand in our library early in September—which furnishes the occasion for the rambling reflections that start off this group of rambling notes.

The anatomical "preparation" so fervently espoused by William Hunter and his contemporaries has, thanks to our greater opportunities for autopsical teaching, become largely outmoded. Not so with the graven image, however. Almost from the beginnings of the printed medical book—from the last quarter of the 15th century, that is—medical authors and publishers have sought to lend greater interest or point to the text by means of illustration. "Good illustrations are to a fine medical article what show-windows are to an outstanding department store . . . medical readers are attracted to an article by the fine pictures and then linger to scan the medical treatise" (Thomas S. Cullen). Whether or not we choose to accept this interpretation without qualification, it undeniably helps to explain the consistent use and development of medical illustration. The non-illustrated medical book today is indeed a rarity.

At first, of course, the medical illustrations were largely pictorial—scenes of dissection. Then came schematic illustrations of the viscera, the eye, and the cranium, sad commentaries on the weight of tradition and the lack of widespread dissection. For pathological anatomy monstrosities largely sufficed. Canano's little work on the muscles (ab. 1541) appears to be the first anatomical work offering illustrations engraved on copper rather than wood. The wonderful Vesalian illustrations (1543) were reproduced from the original wood-blocks by the New York Academy of Medicine in 1934. Vesalius' opponent Eustachius was perhaps the first to use copper engravings in an extended anatomical work (1564). The fascinating story of the development of anatomic illustration can be traced, though not too securely or comprehensively, in Choulant's "History and bibliography of anatomic illustration in its relation to anatomic science and the graphic arts" as translated and edited by Mortimer Frank (1920), one of the most thumbed of our historical reference books.

Our own library could (and has) put on a very fair exhibit illustrating the history of medical illustration from the finished product. It has even two original specimens (one unique) of the work of 17th century medical artists. These are the wonderful series of eighteen specimens of the plates used in Aselli's *De lactibus* (1627), in states progressing from ink sketches to the finished colored woodcut prints. Garrison characterized the Aselli prints as "the first colored anatomic engraving of consequence." The series—which obviously emanates from the atelier of the Aselli illustrator himself—affords a rare glimpse into the actual technique employed in this unusual medium. And, secondly, the thirty folio plates (some of double size) in color, said to be gouache or tempora, illustrating the *De formato foetu* (1604) of Fabricius ab Aquapendente, the larger of the two sets known to exist. These have recently been described by Adelmann in his notable historical contribution, *The Embryological Treatises of Hieronymus Fabricius of Aquapendente* (Cornell University Press, 1942).

The library's collection of the older illustrated anatomies, it is appropriate to observe here, is used a good deal by historians, teachers, and even commercial artists. Our card catalogue has a special section devoted to medical artists, whose names not infrequently appear these days on the title-pages of the books they have illustrated. One of our anatomical Fellows, Dr. Oscar Batson,

annually so inspires his students with his own interest in the historical anatomies that they flock to us to have photostatic copies made from our books for themselves. Recently one of these students appeared at the door of the librarian's office and hesitatingly inquired if, by any chance, he could tell him from what book might have come two old anatomical woodcuts that he had just picked up in one of our old book shops. They were originals from Johannes de Ketham's *Fasciculus medicinae*, Venice, 1495, and he had paid $2.50 for them.

But we do not forget that also the present is the past of the future, as Miss Gertrude Stein might say in one of her more conventional moments. Our Honorary Director of the Department of Medical Art, Dr Samuel B. Sturgis, has as one of his high aims for that department the gathering together of original specimens of the work of our contemporary medical artists. A nucleus has already been formed in a fine collection of the work of the late Erwin Faber. The interest of a distinguished resident medical artist has recently been enlisted, so there is good reason to believe that this collection will be an outstanding one in due course.

Modern medical illustration in this country is, of course, inextricably associated with the name of Max Brödel, who arrived in Baltimore from Germany in 1894, died in 1941, and in the intervening years "revolutionized medical illustrating in the United States and Canada .... No other man who has ever lived has done so much to improve the beauty and accuracy of medical illustration" (Thomas S. Cullen). The exhibit compiled and presented by *Modern Medicine* contains specimens of Brödel's work, of that of some of his noted pupils, and of other distinguished contemporary medical illustrators. It is one that doubtless few physicians will not make a rousing effort to see. From what has been said above, one may probably justifiably assume that the exhibit will feel comfortably at home in the library of the College.

### *The College's Seventh Secretary, Dr Samuel Emlen, Witnesses the Fall of Napoleon and the Peace "Grand Jubilee" in London*

Should one expect a physician to be a more than ordinarily good diarist? His training is such, one would suppose, as to cultivate to a high degree the powers of observation and perception. But, on the other hand, these are directed to fairly defined and limited ends: a patient comes to him with an ailment to be cured; the physician works from symptoms. Sometimes these are obvious and self-explicit; other times, he must observe at length and hope eventually to perceive. In all cases, the observation is economically centrifugal—he uses no more observation and perception than is needed to cure his patient. It seems questionable whether the medically pointed and developed powers of observation and perception translate themselves automatically into a larger frame. If a physician writes an interesting diary (or other non-medical work), are not the chances better that the outcome is dependent on personal qualities, aided perhaps by, but not originating in, his medical training?

Thus, a very great physician may be an unconscionably dull diarist if he be a dull fellow once he steps off the medical reservation; and, per contra, an outstandingly mediocre one may give delight by powers of observation and perception too dimly reflected in his professional work.

Samuel Emlen (1789–1828), the seventh secretary of this College, was a Quaker and an eminent Philadelphia physician. He was at one time secretary to the Board of Health and to the Philadelphia Dispensary, was co-editor of the *Journal of Foreign Medical Science and Literature*, and was active in the organization of the Pennsylvania Society for Discouraging the Use of Ardent Spirits.

In 1812, Emlen, at the age of 23, received his medical degree from the University of Pennsylvania, the subject of his thesis being mania à potu (delirium tremens). No sooner was he graduated than, like so many American medical students of the day, he embarked for England, almost at the moment of the official beginning of the war between Great Britain and the United States. However long he may have intended to stay, he remained abroad for two and a half years.

The library has recently been so fortunate as to receive from Mr. John Thompson Emlen (through a member of the Library Committee, Dr Wiliam N. Bradley), a notebook kept by Samuel Emlen during his sojourn abroad. It is labeled "Notes on a tour through England, Wales, Ireland and Scotland. Note book No. 2." The diary gives a beautiful picture of these countries and their inhabitants as seen by a young Philadelphia Quaker, active, interested, and by no means phlegmatic. A great deal of what he saw—such as filth and abject poverty hitherto unknown to him—he did not like. Youthfully and Quaker-

ishly sententious, he was yet no prude. He observed with considerable disappointment that the Dublin ladies of the higher class did not display "the fine complexion & skin & often beautiful faces of the lower irish emigrating to America"; and he notes, without too much distaste, that "after dinner they [the Irish] pass round the bottle so rapidly, that you are almost compelled to get drunk or give offense".

This is not a diary of exceptional quality, perhaps, but one finds oneself continuing the reading of it despite the handicap of the minute and fading script; one of the chief interests it arouses is that of observing the impressions made by the Old World on an affluent, not too socially conscious, youth of the New.

Unfortunately, the diary has little of professional medical interest in it. But Emlen did have the good fortune to be in Paris at the time of the capture of the city by the Allies, and shortly thereafter in London, during the Peace Jubilee. As we have lived recently through somewhat similar historic events, it may be of interest to read young Samuel Emlen's description of the earlier ones.

## From the Notebook of Samuel Emlen

### *Paris*

"April 3rd 1814. I have for a long time neglected noting occurrences, not because I have not witnessed events enough interesting to claim a place among my memorandums, but because my mind has been so engrossed and agitated with the tragic scenes perpetually passing around me that I have not had enough command of myself to sit down to delineate them.

"The sanguine contest appears at last to be coming to a close. Notwithstanding the powerful resistance made by the Emperor of France to the different repulses with which the coalized powers have met, they have at last entered victorious into Paris! On the 30th of March they appeared before the barriers of this city, an army immense—they say 140,000 men! Resistance, however, was made by about 13,000 French troops on a most advantageous height called Belleville. They had about 60 pieces of cannon. The battle began about half past 6 in the morning and continued till about 5 in the afternoon with dreadful destruction, when the French were forced to retreat and the city was given up by capitulation—a suspension of arms and the white flag hoisted.

"On the morning of the 31st the army entered Paris in perfect order, with the Emperor of Russia, the King of Prussia, the Prince of Schwarzenberg, etc. The crowd in every direction along the boulevards was prodigious. Six or 8 Americans with myself were among them.

"Regretting all the horrors consequent on war, nothing could be more electrifying to the feelings of a spectator than a scene like this. It seemed like a romantic dream. I could hardly convince myself that I had witnessed such an unexpected event. What a reverse for the Emperor Napoleon; after having visited [sic] almost every capital in Europe with his victorious army, behold his downfall! These things are too gigantic for the sober reflection of the human mind. It seems as though the Divine Ruler of events delighted in alternation. In nature all is mutation—from light to darkness, from darkness to light, summer and winter, tempest and serenity, war and peace, life and death, etc. To heroic genius he grants for a time unbounded prosperity, that he may feel at last the full force of instructive adversity. Is it not for mankind to reap the important instruction from these lessons placed before their eyes?

"The troops placed on the banks for the defence of Paris could be distinctly seen from many situations within the city—from the boulevards I saw a number of them myself. The cannons were heard as distinctly as if they had been fired over our heads, as well as the muskets.

"What a most solemn spectacle was Paris on this morning, the 30th. As I walked to the coffee house to breakfast, the doors were all filled with men, women and children listening at the cannon which thundered every instant in our ears; what trembling anxiety was pictured on every countenance; yet such is the heartlessness of the French character, such their insensibility to the impressions which affect the reflecting part of mankind in general that the little emotion which even this dilemma produced was astonishing.

"Since the Allies have entered, however, there has been a decorum as honourable as it was unexpected—no pillaging has been permitted without punishment; the Guard National rest charged with the protection of the citizens. We walk and go where we please in the midst of the army.

"On the 2d of April I walked out with several Americans into the field of battle—here we were traversing the encampment of 30,000 soldiers!

We saw the effects of the cannon in the trees torn to pieces by their force and houses pierced in holes, and walked over the earth where thousands had fell dead but 24 hours before! A Russian officer stated that they lost 62 officers from one charge—from which one may judge the dreadful destruction in the army—indeed the position of the French cannon was such it could not be otherwise. Thirty thousand soldiers encamped was a novel spectacle to all of us. We got through them all and returned safe home, though many had been robbed of their watches, coats, boots, etc., among others, some of our countrymen.

"The Emperor Alexandre rides about Paris in the midst of the acclamations of the populace, who cry "Vive Alexandre", "Vive le roy Louis XVIII," etc. White cockades are mounted by men and women. Louis 18th has addressed the people and is expected in Paris. A provisional government is established with Talleyrand at the head. The senate and corps legislative are still in power and have had several sessions. Declared themselves no longer allied to Napoleon and all soldiers etc. freed from their oath of allegiance. The Emperor Alexandre has granted the liberation of all the prisoners in Russia, more than 100,000. In short, a thousand things transpire now every day, with which the gazettes are filled.

"On the 5th and 6th of April I walked out again in different directions over the field of battle. The effect of such a scene is indescribable. Seven days after the battle we saw hundreds of bodies laying naked in every direction, many of them in a state of putrefaction, killed by many species of wound; heads severed from the body, arms, legs etc. broken in pieces. They were all of the enemy and the poor Frenchmen were busy burying them while we were there and I suppose had been ever since the morning of the 30th. The effects of the cannon bullets astonished us—huge trees were shattered to pieces; through one tree of a large diameter a bullet had passed through and left the appearance of its having been board . . . Houses, windows, walls etc. everywhere shewed the marks of balls and bullets. They were all evacuated, furniture broken and burned. The devastations, the horreurs of war must be seen to be conceived; it is enough to confirm every spectator in the principles of Quakerism.

"We saw about 30 dead bodies all laying naked, unburied in a small garden—smelling most offensively. I examined them all, found a number of them had been operated on and the wounds dressed.

"April 12th Count d'Artois, brother of Louis XVIII, arrived in Paris after an absence of more than 30 years, banished from the French soil at the revolution. All Paris, lining the streets, received him with loud huzzas. He arrived on horseback, dressed in the uniform of the National Guard. He first went to the church, where there was a great ceremony, singing of Te Deum etc., in crowds of tens of thousands.

"The Crown Prince of Sweden, Bernadotte, arrived. Louis XVIII is to sail from the Thames on the 13th for France. The Emperor of Austria is expected in Paris on the 14th. All the world almost is to be seen in Paris. All the Potentates of Europe, and an army composed of nations speaking, 'tis said, ten different languages! Never was a country visited at so interesting a period by a stranger as France at present. Events have never transpired more replete with interest, more magnanimous [sic] since the first pages of history.

"The Emperor Napoleon has placed his signature to a formal resignation of the crown for himself and heirs, and the manner in which he has worded it is another singular trait in the character of this singular *genius*. He has accepted, 'tis said, 6,000,000 of francs per annum and the Isle of Elbe as his residence. Can such a character be confined; can he live in obscurity? I have seen him frequently, but I have a great desire once more to peep at his physiognomy. It is said his countenance and manner is unchanged. Europe has once more tranquillity. Nothing was wanted more. Nothing could be more acceptable. France called aloud for peace. God grant its continuance.

"May 15th. Louis XVIII entered Paris. The ceremony was attended with all the consequential extravagance that can be conceived. The streets through which he passed were lined on each side with the Guard National as thick as they could stand to keep off the press of the mob. The houses were lined with all kinds of tapestry adorned with flowers etc., the windows filled with women and children shouting "Vive le roi" etc. His escort consisted of the marshals, generals, troops of infantry—part of the old imperial guard—guard national, cavalry and infantry, etc., without end.

"At night there was an universal illumination, fire works on the bridges etc. The day after his

arrival, the Emperor of Russia, the King of Prussia, Emperor of Austria with all their etat major rode to the Tuileries, where there was a review of Russian troops. I had a fair view for some time of their three majesties.

"At the entrance of the king, the shouting of "Vive le roi" etc. from the windows and streets (who were all women and children) was returned by the national guard and others in the escort with great vehemence—but not a single shout could they get from the old imperial guard! Their martial countenance, with huge mustachios, was enough to strike terror by their very looks. They looked angry and revengeful though dejected—a dark, gloomy and ferocious face. The Frenchmen, as they passed along, seemed to be pitying them with a sigh. Old veterans whom Napoleon had led victorious into every quarter of Europe, who had fought campaign after campaign, and whose valor in battle was acknowledged by all who fought against them to be irresistible. I have heard it said by many, that the very sight of these old guards and their shouts of "Vive l'Empereur!" which always preceded their rushing charge upon their enemies, has struck terror at once in the opposing army, that they have as if involuntarily thrown down their arms and on their knees supplicated for quarter, without firing a gun! . . .

*London and the Peace Jubilee*

"June 14th. I once more entered the smoke of London, which I had hoped I never again should take into my lungs. I found the people all crazy with their sovereign visitors, the Emperor of Russia and King of Prussia. It was astonishing what immense crowds collected to get a peep at them. Nothing can be more noisy, dirty, insolent and offensive than a London mob upon such occasions . . . .

"Aug. 1st . . . . The general thanksgiving day which occurred some weeks past was a display of great state and splendor. The Regent and members of both Houses of Parliament went in state to St. Paul's. The crowd collected was as great as to see the two sovereign strangers. London has been indeed a scene of bustling confusion. It was the only time to see what a dirty rabble composes the great mass of its population. I had as leave hang myself as get in the midst of such an unruly, dirty set. As much as 20 guineas was given in many places for a window to look out of at these different spectacles. I had seen so much of them I had no inclination to see more.

"Today was the Grand Jubilee for celebrating the peace, for which great preparations at an immense expense have been so long making. Twenty-two small vessels built for the purpose were put upon a pond in Hyde Park to represent a naval engagement. A temple and chinese bridge were constructed in St. James's Park to exhibit fine works.

"The day was appointed a holy day, and the crowds collected were no doubt larger than were ever seen assembled. I got into Hyde Park and saw part of the naval battle between vessels with the English and Americans. Of course the American flag was soon struck in the midst of the thundering cannon, or rather, pop guns. There was loud shouting against the Yankees. It might have represented the battle on Lake Erie in miniature, had they have struck other flags. It was a footy, childish affair and there was little to excite interest except the noise. I was glad to get out before night alive.

"The park was filled with tents and shops; drinking, swinging, gaming etc. formed their sport. Almost all classes have cried out against this useless, childish expense. The opposition papers have been very witty upon it . . ."

And so we see our young secretary-to-be, with his pacifist, sheltered background suddenly plunged into the midst of one of the great historic events of the world; in France, in the British Isles, in Holland observing conditions and modes of life far removed from those of his native West Chester and Philadelphia. As a Quaker, he was easily confirmed in the principles of Quakerism by his glimpse of the *horreurs* of war; as a vigorous young man, he responded to the magnetism of the Emperor Napoleon and the romantic aura surrounding his legendary feats—without for a moment realizing, evidently, that these emotions were logically incompatible. He saw much that was ugly in social conditions; though he knew the word 'tragic', throughout the diary the emotion of pity is rarely exhibited, still less any questioning of causes. Emlen was no Tom Paine, but we are grateful for a diary that brings the scenes and persons and events of his *Wanderjahre*—momentous years—vividly to life, and while so doing makes us better acquainted with one who was a secretary of the College when it, too, was in its youth.

### *A Harvey Cushing Rarity*

Harvey Cushing, of course, needs no introduction to either the world of science or that of historical letters. His posthumous monuments in the latter field are the recently published catalogue of his library and his bio-bibliography of Vesalius, both *in lucem prodita* by his spiritual heir, Dr John F. Fulton. The biography of Cushing now being composed by Prof. Fulton will doubtless do for Cushing what the latter did for Osler—fully document the many facets of his genius. What may be regarded as something in the nature of a by-product of the biography in progress is a little publication just issued in a limited edition by the Rowfant Club, Cleveland, again with the assistance of Prof. Fulton.

"A Visit to Le Puy-en-Velay, an Illustrated Diary by Harvey Cushing" records a ten-day trip made in 1900, when Cushing was thirty-one years old. It is one of several diaries left by Dr Cushing; the others, Fulton explains in his *Introductory Note*, are being used in connection with the biography.

The Le Puy-en-Velay diary is brief, 35 pages sufficing for the text and a profusion of illustrations —sketches, water colors, photographs. The text may possibly disappoint those anticipating a greater degree (or perhaps only a different quality) of the gay, artistic spontaneity described in the introduction as characteristic of the diaries. The illustrations have the delicacy, subtlety, and precision that one would expect from the hand of Harvey Cushing; there seems not to be a superfluous touch of pencil or brush in any of them. The documentary material (presumably supplied by Prof. Fulton) is beautifully calculated to give the reader the background information he is likely to wish for, and the little book is charmingly produced from a technical standpoint. Admirers of Cushing will treasure it as a rare bit of Cushingiana.

### *Postage Stamps Commemorating Austrian Physicians*

What is there about postage stamps that tends to turn an honest, upright, forthright, noble citizen into a furtive, devious, sometimes unwontedly aggressive creature of whom one must be wary? Leave an envelope with an interesting looking foreign stamp on your desk while you are talking matters of state with a supposedly perfectly normal person. If you notice that his mind suddenly seems to be wandering, his face and hands twitching, his eyes becoming fixed, his chair imperceptibly moving closer to your desk, the diagnosis is easy, prompt action indicated. He will not want the stamp for himself, mark you, but for his son, his grandson, his nephew, or his grandmother—but he will want it and he will get it, unless you feel it necessary for some reason to be extremely unpleasant about it.

In the good days before the war, when steady waves of the foreign periodicals were coming in, our current-periodicals assistant's lot was not an entirely happy one. During one notable period there was, on the one hand, the distinguished president of the College himself; on the other, the assistant superintendent. Trailing them, no whit abashed by such formidable competition, was a little band of hopefuls, Fellows and non-Fellows, tremblingly poised for a kill. Wastebaskets were ransacked, covers mutilated, the smoke of battle filled the air.

Now, the probably little-known crux of the matter is that the library is in the stamp-collecting business too. The medico-historical postage-stamp collection will be found in Dr Sturgis' generously inclusive Department of Medical Art, where it, of course, belongs. This little collection —like that of book-plates—has been rather a stepchild in recent years, but with the world opening up to us again, it behoves us to capitalize on our excellent opportunity to augment it in the economic manner God has provided us, and to devise some Bretton Woods arrangement whereby, after the library's interests have been safeguarded, the remains may be made available to these stamp-collecting wolves without prejudice to the fair name and works of the assistant in charge of the incoming periodicals.

The occasion for these remarks (not so ill-tempered as they may sound to the guilt-conscious) is the recent receipt (from our Fellow Dr G. N. J. Sommer, of Trenton) of an interesting series of stamps commemorating famous Austrian physicians, issued in 1937, the year before the late *Anschluss*. The nine stamps honor the following: the ophthalmologist Ferdinand von Arlt (born in Bohemia, Austria-Hungary), in his latter years, professor of ophthalmology at the University of Vienna; Auenbrugger (born in Styria, Austria-Hungary), of *Inventum Novum* fame; the famous surgeon Billroth (born on the island of Rügen in the Baltic Sea); the dermatologist Ferdinand von Hebra (born in Moravia, Austria-

Hungary); the anatomist Joseph Hyrtl (a Hungarian by birth); the neurologist-psychiatrist Theodor Meynert (born in Dresden); Rokitansky (Born in Bohemia), professor of pathological anatomy; Joseph Skoda (also a Bohemian), leading clinician; and the famous Leyden-born surgeon and clinician Gerhard van Swieten.

Thus, of these famous "Austrian" physicians, none was born in Vienna, the city with which their names are so closely associated, and four were not even native Austrians. This issue is, in effect, a high and deserved tribute to the magic of the beautiful city on the Danube which for so long was mistress of European medicine and culture. Our neurologists and psychiatrists may be interested to know that the honor of the highest denomination (64 *Groschen*) in this philatelic Hall of Fame goes to their candidate, Theodor Meynert, next to Hyrtl, the most recently dead of the group. Perhaps because he has been the longest with his ancestors, van Swieten comes the lowest (5 *Groschen*). *Sic transit!*

*The Voynich 'Roger Bacon' Manuscript Again*

A brief communication to *Science* (June 15, 1945, p. 608) by Leonell C. Strong, of the Yale University School of Medicine, dramatically re-opens a *cause célèbre* of a quarter of a century ago in which the College figured as one of the well-intentioned, if perhaps too little cautious, principals.

At a special meeting of the College on April 20, 1921, William Romaine Newbold, then Adam Seybert professor of intellectual and moral philosophy at the University of Pennsylvania, delivered, as The Mary Scott Newbold Lecture V, a lecture entitled, "The Voynich Roger Bacon Manuscript." For four or five months previously, the press had been extending itself in spreading an air of mystery about, and hinting at the remarkable contents of, this manuscript in cipher which Prof. Newbold was known to be decoding. Mr Wilfred Voynich, the dealer in rare books who owned the manuscript,[1] was quoted as saying, "I cannot tell now where or how I acquired the manuscript, but I can say that rumors to the effect that it was stolen by the Germans at Louvain is [*sic*] untrue. The manuscript was in my possession in 1912."[2] Again, "I would not dare take it to certain cities. The danger of theft there would be too great . . . I would never take it to Paris.[3] I am in the relation of a janitor to this manuscript although I own it. It is in a true sense the property of the world, and particularly of all persons of scientific mind."[4] Though the value of the manuscript was placed at something more than $100,000, it was said, it was insured for a greater sum. Perhaps it need not be added that Mitchell Hall was well filled for the notable occasion on which Prof. Newbold gave to the world the first fruits of his long study of the manuscript. The lecture was then published in our *Transactions* of that year.

Correspondence in the library archives[5] between our then president, Dr William J. Taylor, and Prof. Newbold indicates that there was a degree of entirely amicable rivalry between the College and the American Philosophical Society over the question of which was to have the honor of hearing the first pronouncements from Prof. Newbold. As neither institution cared to make an issue of it, the decision was left to the lecturer, who preferred to make his general report first and before the larger audience which it was expected the College would provide, and to reserve for the more esoteric audience of the Philosophical Society the technical explanation of the ciphers. Accordingly, the latter was given at the annual meeting of the Society on the day following the lecture at the College.

Correspondence[6] between Dr Taylor and Mr Voynich shows that the latter at first declined an invitation to precede Prof. Newbold's College lecture with an account of the "history and peregrinations" of the manuscript. Subsequently he relented, and his account precedes the Newbold lecture in our *Transactions*. Both were freely utilized, of course, in Newbold's posthumous "The Cipher of Roger Bacon" (University of Pennsylvania Press, 1928), edited by his devoted colleague at the University, Prof. R. G. Kent.

[1] It was from Mr. Voynich, incidentally, that the library purchased, in 1922, the *Contra pestem* of Johannes Mercurius Corrigiensis—an alleged incunable of similarly mysterious origin which we reprinted, with translation and a bio-bibliography, in the *Transactions & Studies*, 4. ser., vol. 9, 1941–2.

[2] *Public Ledger*, Phila., April 3, 1921. Clipping in library files (ZZ1a 78).

[3] In his Foreword to Newbold's "The Cipher of Roger Bacon," Prof. Kent writes (p. xiv), "Mr. Voynich in 1912 exhibited this manuscript to French scholars in Paris. . . ."

[4] *The Philadelphia Inquirer*, Jan. 6, 1921. Clipping in library files (ZZ1a 78).

[5] ZZ1a 78.

It may be wondered how the College came to be selected as the forum for a lecture by a professor of intellectual and moral philosophy on a manuscript supposedly written by Roger Bacon.[6] Apart from any possible nepotistic reasons, there was an ample reason in the manuscript itself as its contents appeared to Prof. Newbold:

"The manuscript falls into four divisions, dealing respectively, with plants, the heavenly bodies, the generation of animal life and the preparation of drugs. The common link connecting all four is probably Bacon's interest in the prolongation of human life. Plants are discussed because of their medicinal properties; the stars because they determine a man's character at his birth and influence him throughout life; embryology because of the bearing upon later life of all factors influencing conception, and pharmacology because drugs are essential to the cure of disease."[7]

Now, unfortunately, Prof. Newbold's researches were not unanimously acclaimed. In *Harper's Magazine* for July, 1921, the late Prof. John M. Manly, an authority on early English literature, expressed some scepticism concerning Newbold's system of ciphers. George Sarton, commenting in *Isis*[8] on Manly's article, concluded with the statement, "I share fully his scepticism." On the publication of "The Cipher of Roger Bacon", in 1928, Sarton returned to the attack. Crediting Newbold with complete honesty, he termed him, "as gently as possible", a self-deceived enthusiast. "I was hoping then [1921]", he wrote, "that this idiotic thing might be averted, but now that it has been published in book form . . . a new stream of evil has been started which will work mischief for ages to come. We may be sure that there will be enough cranks to continue the new kind of aberration originated by Newbold, and enough misguided occultists and muddle-headed people of various kinds to stimulate them. Henceforth when we shall speak of Baconian fools, we shall have to distinguish between two groups of such fools, the Francis Baconians and the Roger Baconians."[9]

However great the dissatisfaction with Newbold's attempt to solve the enigma of the cipherous Voynich manuscript, characterized by Manly as "the most mysterious manuscript in the world", (the title of his *Harper's* article), there still remained the problem of finding the key to the cipher and identifying the author. In the past year, one writer has dated the manuscript as post-Columbus on the basis of its reference to two plants unknown to the Europeans before the return of Columbus from his second voyage.[10] And now comes the startling announcement that the key to the cipher has been determined and that the author—Anthony Ascham, *fl.* 1533—is named (in cipher) on folio 93.

Strong writes: "The text, so far decoded, is in Medieval English [Newbold and others supposed it to be in Latin] and deals with (1) the effects of plants on physiological processes in health and disease, especially the diseases of women, and (2) a conception of pre-Harveian generation and parturition." In conclusion Strong pleads that the complete manuscript, or a photostatic copy of it, be made available to him. It is understandable that, entertaining a hope of being able to decode the whole work, he should find it undesirable to publish the details of the key at this time; the ubiquitous "present war conditions" need not have been trotted out to do service again. Meanwhile, this "most mysterious manuscript in the world", which has caused so much controversy, presumably reposes still as part of the undisposed-of part of the Estate of the late Mr Voynich.[11] Let us hope that in time it will find fairer fame as the Voynich Anthony Ascham Manuscript and be as useful to students of 16th century medical thought as our quondam Newbold Lecturer hoped it would be to those of the thirteenth.

W. B. McD., 2d

[6] Not, of course, if one appreciated the fact that Bacon was a writer on medical, among other, subjects.

[7] *The Evening Bulletin*, Phila., April 21, 1921, reporting Newbold's lectures before the College and the American Philosophical Society. The lecture as published in the *Transactions* mentions five divisions and amplifies the matter in this paragraph considerably.

[8] Vol. 4 (1921–22), p. 404. See also Manly on the Voynich manuscript in *Speculum, 6,* 345, 1931; cited by Strong, who gives the date incorrectly as 1921.

[9] *Isis, 11,* 141–5, 1928.

[10] Hugh O'Neill, *Speculum, 19,* 126, 1944. Cited by Strong.

[11] At least, it is listed in de Ricci and Wilson's *Census of Medieval and Renaissance Manuscripts in the United States and Canada*, vol. 2, p. 1846, 1937, as then being still held by the Estate.

# Transactions of the Sections

## SECTION ON GENERAL MEDICINE

*Joint Meeting, January 22, 1945*[1]

MALARIA TODAY AND TOMORROW. Julia Morgan, M.D.

SOME PRACTICAL CONSIDERATIONS IN THE CONTROL OF MALARIA. Garfield G. Duncan, Col.,(MC).

*Stated Meeting, February 26, 1945*

INSULINOMAS, BENIGN AND MALIGNANT. Joseph T. Beardwood, Jr., M.D., Joseph C. Yaskin, M.D., and Walter Estell Lee, M.D. (Commentator: Edward S. Dillon, M.D.)

METABOLIC CHANGES IN PATIENTS WITH CANCER OF THE GASTROINTESTINAL TRACT. George T. Pack,* M.D.

*Stated Meeting, March 26, 1945*

THE PRIMARY INFLUENCE OF BASAL VASCULAR TONE ON POST-OCCLUSIVE COLLATERAL CIRCULATION AND IN SELECTING PATIENTS FOR SYMPATHECTOMY. Meyer Naide, M.D., and Ann Sayen. (Commentator: Francis C. Grant, M.D.)

HYPERTROPHIC PYLORIC STENOSIS IN ADULTS. J. Edward Berk, Capt.,(MC). (Commentator: Jonathan Rhodes, M.D.)

STREPTOMYCIN FOR TYPHOID FEVER. Hobart A. Reimann, M.D., William F. Elias, Ph.D., and Alison H. Price, M.D. (Commentator: H. A. Zintel, M.D.)

CLUBBED FINGERS. Robert Charr, M.D., and Paul C. Swenson, M.D. (Commentator: John Q. Griffith, Jr., M.D.)

*Joint Meeting, April 23, 1945*[2]

BOECK'S SARCOID AND SYSTEMIC SARCOIDOSIS. David Reisner, M.D.

*Joint Meeting, May 21, 1945*[3]

FERTILIZATION AND EARLY GROWTH OF THE HUMAN EGG.[4] John Rock, M.D.

[1] With the College's Section on Public Health.

* By invitation.

[2] With the Laennec Society of Philadelphia.

[3] With the Philadelphia Urological Society.

[4] The annual B. A. Thomas Oration of the Philadelphia Urological Society.

## SECTION ON OPHTHALMOLOGY[5]

*Stated Meeting, January 18, 1945*

ACQUIRED PTOSIS, CLASSIFICATION AND CORRECTION. Edmund B. Spaeth, M.D.

CONCERNING ABERRATIONS OF THE EYE. Alfred Cowan, M.D.

INFECTION OF THE HUMAN ORBIT WITH TORULA HISTOLYTICA. Charles Weiss,* M.D.

*Stated Meeting, February 15, 1945*

THE IMPORTANCE OF THE FIXATING EYE. James W. White,* M.D.

*Stated Meeting, March 15, 1945*

TRAUMATIC IRIDODIALYSIS, ITS SURGICAL CORRECTION: REPORT OF A CASE. A. Barlow,* M.D., and Herman L. Weiner,* M.D.

REVALUATION OF THE HERBERT OPERATION FOR GLAUCOMA. Louis Lehrfeld, M.D.

SYMMETRICAL DEFECTS IN THE LOWER LIDS ASSOCIATED WITH ABNORMALITIES OF THE ZYGOMATIC PROCESSES OF THE TEMPORAL BONES. Irving H. Leopold, M.D., Francis Mahoney,* M.D., and Mabel Lee Price,* M.S.

PENICILLIN THERAPY OF VITREOUS INFECTIONS. Irving H. Leopold, M.D.

*Stated Meeting, April 19, 1945*

CONSERVATION OF LID MARGINS DURING BLEPHAROPLASTY. Charles A. Rankin, M.D.

ANGIOID STREAKS OF THE FUNDUS OCULI: REPORT OF A CASE OBSERVED OVER A PERIOD OF 36 YEARS. William Zentmayer, M.D.

SOME FACTORS IN THE EXAMINATION OF ASTIGMATISM. I. S. Tassman, M.D.

## SECTION ON OTOLARYNGOLOGY[6]

*Joint Meeting, January 17, 1945*[7]

INTRODUCTION OF AN ARTISTIC VIEWPOINT IN RHINOPLASTIC DIAGNOSIS. Jacob Daley, M.D.

[5] The transactions of this Section are customarily abstracted in the *American Journal of Ophthalmology* and the *Archives of Ophthalmology.*

[6] The transactions of this Section are customarily abstracted in the *Archives of Otolaryngology.*

[7] With the Philadelphia Laryngological Society.

(Commentators: Henry A. Miller, M.D., and Romeo A. Luongo, M.D.)

The Use of Penicillin in Chronic Otitis Media. John J. Conley, Capt., (MC), A. U. S. (Commentator: George M. Coates, M.D.)

Open Safety Pin in Esophagus, with Perforation of Pericardium. William A. Lell, M.D. (Commentator: Gabriel Tucker, M.D.)

Kodachrome Cinematography of Upper Respiratory Tract: a Motion Picture. S. Eugene Dalton, M.D.

*Joint Meeting, February 21, 1945*[7]

Neuralgic Syndromes of the Head, Their Diagnosis and Treatment. Rudolph Jaeger, M.D. (Commentators: Francis C. Grant, M.D., Joseph C. Yaskin, M.D., and Karl M. Houser, M.D.)

*Joint Meeting, March 21, 1945*[7]

The Receptor Apparatus of Vestibulo-vasomotor Reactions. J. R. Lindsay, M.D., M. J. Oppenheimer, M.D., H. T. Wycis, M.D., and E. A. Spiegel, M.D. (Commentator: Matthew S. Ersner, M.D.)

Planning the Rhinoplasty. Samuel Cohen, M.D.

Muscle Spasticity in Functional Aphonia and Dysphonia. Hertha Tarrasch, M.D. (Commentator: Emily Van Loon, M.D.)

An Animated Motion Picture on Naso-plastic Surgery. Albert P. Seltzer, M.D.

*Joint Meeting, April 18, 1945*[7]

Otolaryngology in Latin America. Chevalier L. Jackson, M.D.

Otolaryngology in Portugal. Jose dos Santos, M.D.; *in* Puerto Rico. William Reichard, M.D.; *in* Peru. Lorenzo Morelli, M.D.

Medicine in Latin America As Related to Otolaryngology. Aristides A. Moll, Ph.D.

## SECTION ON PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE

*Joint Meeting, January 22, 1945*[8]

*Joint Meeting, April 16, 1945*[9]

Symposium on Tuberculosis Control

The National Program. Herman E. Hilleboe, M.D.

Tuberculosis Control in Philadelphia. Katherine R. Boucot, M.D.

(Commentators: Martin J. Sokoloff, M.D., and W. Edward Chamberlain, M.D.)

[8] With the College's Section on General Medicine. For program, see above under that Section.

[9] With the Philadelphia County Medical Society's Section on Industrial Health.

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TRANSACTIONS & STUDIES

*of the*

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# Recent Advances in Knowledge of the Rh Blood Factors, with Special Reference to the Clinical Applications*†

*By* ALEXANDER S. WIENER, M.D., F.A.C.P.

IT IS indeed an honor to have been awarded the Alvarenga Prize for 1945, and I greatly appreciate the kind invitation to come here to address such a distinguished assemblage of my fellow-physicians. While I am grateful for this tribute to my small contribution to scientific knowledge, the main significance of the decision of the College is that the field of blood grouping has now fully matured and assumes its position with other important branches of medicine. In this presentation I shall summarize some of the recent developments in the subject of the Rh blood factors and their significance for clinical medicine.

Almost every important scientific discovery has a long historical background. Intimately associated with the history of the Rh blood factors is the name of the late Dr. Karl Landsteiner, with whose great achievements all of you are undoubtedly already familiar. Dr. Landsteiner is correctly known as the father of blood grouping, and in 1930 he was awarded the Nobel Prize in Medicine primarily for his discovery of human blood groups which made possible the safe transfusion of blood. Early in his studies Dr. Landsteiner conceived the existence of numerous serologic differences in human blood which might some day make possible the individual identification of persons based on their blood reactions, in a manner somewhat similar to the use of fingerprinting. The discovery of the subgroups in groups A and AB by von Dungern and Hirzsfeld in 1910, and of the properties M, N and P in 1928 by Landsteiner and Levine increased the number of subdivisions of human blood from four to thirty-six, and that was the status of the subject when I began my first studies on blood grouping in collaboration with Dr. S. H. Polayes in 1929. As a result of my interest in blood grouping I became intimately acquainted with Dr. Landsteiner. Our first meetings soon blossomed into a close friendship which continued until his untimely death in 1943, depriving me of an irreplaceable friend and teacher, and the medical world of one of its leading scientists.

Some of the earlier investigations on additional factors in human blood, besides A, B, M, N, and P, did yield findings supporting Landsteiner's idea of the existence of numerous individual differences in human blood. However, attempts to reproduce these results were not consistently successful because no satisfactory method could be devised for preparing the necessary antisera. In 1937, I became interested in the evolution of the agglutinogens M and N, and when my preliminary findings

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† From the Serology Laboratory in the Office of the Chief Medical Examiner of New York City, and the Blood Transfusion Division, Jewish Hospital of Brooklyn, New York.

proved significant, I continued the work in collaboration with Dr. Landsteiner. In the blood of rhesus monkeys we detected the presence of M-like agglutinogens, and we also found that the injection of the blood of rhesus monkeys into rabbits stimulated the production of anti-M agglutinins. Previously it had been found by Schiff that injections of sheep blood into rabbits caused the formation of anti-A agglutinins and hemolysins. It therefore occurred to us that by continuing this line of research, namely, the use of animal blood instead of human blood for preparing our antisera we might discover new factors in human blood. Indeed, we did find that some of our antisera for rhesus monkey blood contained an agglutinin reacting with the blood cells of 85 per cent of the white population, independently of the blood groups or M, N and P factors. The new factor detected by these rhesus antisera we later designated as Rh to indicate the manner in which it had first been discovered (1).

We did not immediately report our findings because we wished to perfect the method of producing the antisera. When in 1939 Dr. H. Raymond Peters and I encountered three cases of hemolysis following transfusions of blood of the homologus groups, which we proved were due to isoimmunization to the rhesus factor, it became evident that the new blood factor was of clinical importance (2). This is the reason why the Rh factor found by Landsteiner and myself in 1937 was first announced by us in January, 1940.

As already mentioned, the blood cells of 85 per cent of all white individuals are agglutinated by the anti-rhesus sera. Such individuals are said to be Rh positive, while the remaining 15 per cent are said to be Rh negative. These two types of blood are hereditarily determined (3), the Rh factor being transmitted as a single Mendelian dominant by a pair of allelic genes, *Rh* and *rh*. Since every individual possesses a pair of genes from every series of allelic genes, one gene being derived from the mother and the other from the father, there are three genotypes possible. Rh-negative individuals belong to genotype *rhrh* and are always homozygous; Rh-positive individuals may either be homozygous (genotype *RhRh*) or heterozygous (genotype *Rhrh*). Therefore, two Rh-negative parents can only have Rh-negative children. If one parent is Rh negative, and the other is Rh positive, the children will all be Rh positive if the Rh-positive parent is homozygous, or half the children will be Rh positive and half Rh negative, if the Rh-positive parent is heterozygous. When both parents are Rh positive, all the children will be Rh positive, except when the parents are both heterozygous, in which case one fourth of the children will be Rh negative (3).

Natural Rh isoantibodies have never been demonstrated in human serum. Therefore, Rh-negative individuals can be safely transfused with Rh-positive blood provided that they have not become sensitized to the Rh factor as a result of previous exposure to the Rh antigen. The situation with regard to Rh in relation to blood transfusion is therefore different from that which exists for the blood groups, where every individual (except in infancy) has agglutinins in his or her serum for those agglutinogens, A, B or both, lacking from the erythrocytes, so that even a first transfusion of blood of an incompatible group may cause a hemolytic reaction. The clinical importance of property Rh depends on the fact that Rh is a far better antigen in man than M, N and P, as evidenced by the observation that as many as 90 per cent of cases of intragroup transfusion hemolysis can be traced to the Rh factor (4).

Rh-negative individuals may become sensitized to Rh antigen in one of two ways: (1) Sensitization may result from a transfusion of Rh-positive blood or (2) in women, sensitization may result from pregnancy with an Rh-positive fetus. Individuals sensitized by either of these two methods may have a serious hemolytic reaction if transfused with Rh-positive blood. Ideally, therefore, every patient who is to be given a blood transfusion should be tested for the Rh factor as well as the blood group, and Rh-negative patients should only be given Rh-negative blood. Under battle conditions, of course, this precaution is hardly ever necessary because the casualties are mostly men who have never had a previous blood transfusion; in fact, it is undesirable because insistence on Rh tests will unduly delay a life-saving procedure. In civilian hospitals such tests should be insisted on for all patients requiring a series of transfusions, and, if possible, for all female patients, particularly during the child-bearing age. It is important to mention at the outset that not every Rh-negative person receiving transfusion of Rh-positive blood or bearing an Rh-positive fetus becomes sensitized to the Rh factor. Individuals differ in the ease with which they can be sensitized, probably depending on some hereditary constitutional quality, so that on the average only one among approxi-

mately 25 Rh-negative persons exposed to the Rh antigen becomes sensitized.

Soon after the importance of the Rh factor as a cause of intragroup transfusion hemolysis was pointed out by Wiener and Peters, Levine and his collaborators noticed that intragroup transfusion reactions occurred with exceptional frequency in women who had had stillbirths or infants with erythroblastosis fetalis (5). This suggested that isoimmunization in pregnancy might be the basis of the latter disease, which Diamond, Blackfan and Baty had previously shown to comprise a number of syndromes, namely, icterus gravis neonatorum, hemolytic anemia of the newborn, hydrops fetalis and certain unexplained stillbirths. According to the theory of Levine, et al. (6), an Rh-negative woman bearing an Rh-positive fetus becomes sensitized to the Rh factor and the Rh antibodies produced by her pass through the placenta into the fetal blood circulation and combine with the red cells, giving rise to one or another manifestation of the disease. In support of this theory may be cited Levine's observation that in 90 per cent of the cases the mother is Rh-negative while, as already mentioned, only 15 per cent of individuals in the general population are Rh-negative. Again, in about one half of the cases anti-Rh agglutinins could be demonstrated in the mother's serum, proving that she has been sensitized to the Rh factor. In view of this evidence concerning the nature of the disease, the name has been changed from erythroblastosis to hemolytic disease of the fetus and newborn, or congenital hemolytic disease, and the latter name will be used henceforth in this lecture.

While the mating of Rh-negative women with Rh-positive husbands occurs in one of 10 marriages, congenital hemolytic disease affects only one in about 250 newborn. This suggests that only about 1 in 25 Rh-negative women becomes sensitized when bearing an Rh-positive fetus, just as in sensitization by blood transfusion. The first-born is rarely affected, because it takes at least one pregnancy and sometimes more before a sufficient degree of sensitization develops. In most of the rare cases where the first-born was affected, a careful history revealed that the woman has previously received a transfusion of Rh-positive blood. This serves to emphasize the importance of performing Rh tests before giving blood transfusions to women in the child-bearing age, and even to young girls, because such a transfusion could ruin a woman's chances of having a normal child.

While the theory of Levine et al. accounts for many of the essential facts in the pathogenesis of congenital hemolytic disease, a number of apparent paradoxes remain to be explained. Since the intact villus is impermeable to erythrocytes, it is not clear how the fetal Rh antigen gains access to the maternal circulation. Despite the assertions of certain workers, there is no convincing evidence that Rh antigen exists in soluble form in body fluids, as is the case for the A and B factors. The most plausible explanation is that during labor and delivery, villi become detached and enter the maternal circulation, carrying along enough fetal red cells to incite antibody formation by those women who are constitutionally predisposed. Autopsies on women who died in childbirth or shortly thereafter have actually revealed the presence of Langerhans giant cells and villi in the lung bed. At the same time, this would explain why congenital hemolytic disease rarely affects the first-born unless the mother has been previously sensitized by blood transfusion. It is difficult to reconcile Levine's theory with the lack of correlation between the titer of anti-Rh agglutinins in the maternal serum and the severity of the disease in the infant. Thus, in some of the most severe cases of congenital hemolytic disease no Rh agglutinins are detectable in the maternal serum; on the other hand, some Rh-negative women with anti-Rh agglutinins in their serum have given birth to apparently normal Rh-positive infants. The occasional occurrence of congenital hemolytic disease when the mother is Rh positive has been attributed to subtypes of Rh and to the Hr factor, as will be explained later, and some cases have also been attributed to isoimmunization to the A-B blood groups factors. With regard to the common blood groups, it was not clear until recently why the A-B factors so rarely cause trouble, considering that the maternal serum frequently contains natural isoagglutinins anti-A and anti-B, and besides A and B are far more potent antigens than Rh. The suggestion that non-secretor infants are the only ones affected did not seem probable *a priori* because as many as 15 per cent of all individuals are non-secretors, while these cases are uncommon. Besides, in two cases recently seen by the speaker both infants proved to be secretors. Another puzzling feature of congenital hemolytic disease not explained by Levine's theory is why frequently infants appear perfectly normal when

born, yet within a few hours or days severe jaundice and anemia develop.

These paradoxes have been explained by the recent discovery that more than one variety of Rh antibodies are produced by individuals sensitized to the Rh factor (7, 8). In addition to anti-Rh agglutinins, antibodies designated "blocking antibodies" and/or "glutinins" are produced and these antibodies are far more important than the agglutinins in the causation of congenital hemolytic disease. The reason why the blocking antibodies and glutinins were not found previously is that special techniques had to be devised for their detection, as will now be explained.

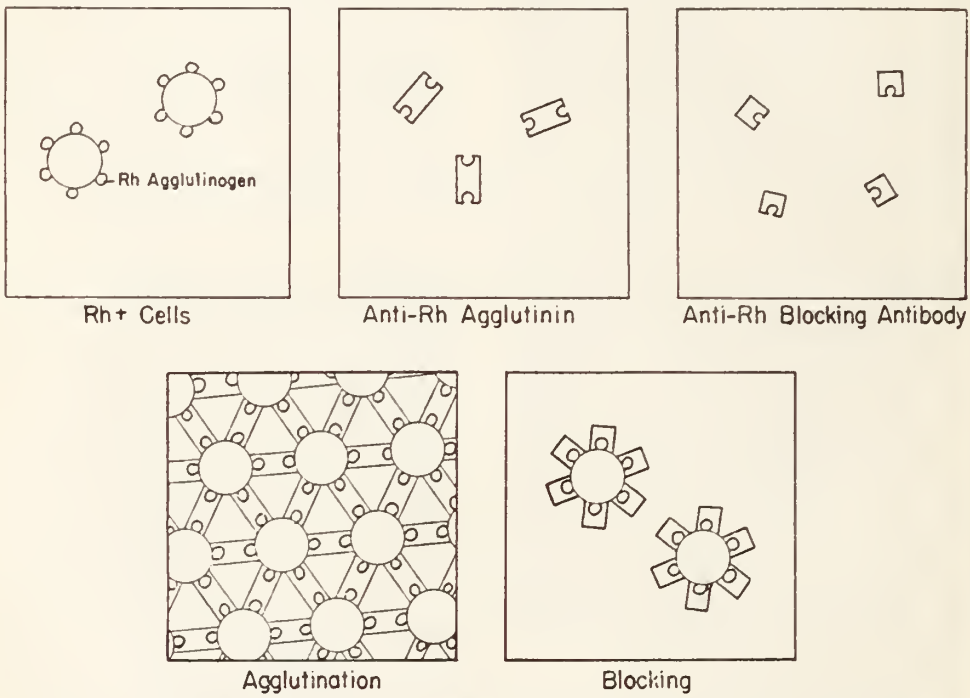


FIG. 1. DIAGRAMMATIC REPRESENTATION OF Rh AGGLUTINATION AND BLOCKING REACTIONS

## TESTS FOR Rh SENSITIZATION

*Agglutination Test* (*9*). In the agglutination test for Rh sensitization a drop of the patient's serum is mixed with a drop of a 2 per cent saline suspension of group O Rh-positive cells in a small test-tube, and the mixture incubated in a water-bath at body temperature (or the temperature optimal for the serum) for 30 to 60 minutes. The reactions can usually be judged from the appearance of the sediment at the bottom of the tube. The sediment is then gently dislodged by twisting the tube and the mixture examined for the presence or absence of agglutination. In positive reactions the red cells are clumped together in large masses usually visible to the naked eye, while in negative reactions the mixture remains homogeneous with each red cell separate and distinct, as proved by microscopic examination. When the patient's serum contains only very small quantities of Rh agglutinin, centrifugation may be necessary to bring out the reaction. When enough agglutinin is present, on the other hand, strong clumping will occur even in tests with the patient's serum diluted with saline solution, and in tests on slides as well as in tubes.

According to our present concept, Rh agglutinins like other antibodies in general are modified serum globulins. Moreover, Rh agglutinins like other hemagglutinins and bacterial agglutinins are presumably polyvalent (probably bivalent) so that each antibody molecule has more than one specific combining group for the corresponding Rh hapten. Since the red cells presumably have numerous Rh haptens distributed over their surfaces, when agglutinin and agglutinogen combine clumping results from the formation of a lattice-work, in accordance with Marrack's hypothesis (cf. figure 1). This concept of the

nature of Rh agglutinins is useful in explaining the pathogenesis of congenital hemolytic disease, as will be pointed out later on.

*Blocking Test* (7). In searching for an explanation of cases of congenital hemolytic disease which were typical except that the maternal serum contained no demonstrable Rh agglutinins, it occurred to me that Rh antibodies might be present but of a special variety incapable of bringing about agglutination. If such antibodies were allowed to combine with the Rh-positive red cells, then the cells might be expected to lose their capacity to agglutinate upon the further addition of anti-Rh agglutinating serum. In preliminary experiments carried out by me in 1941 some encouraging results were obtained, but final proof of the existence of such special antibodies, designated as Rh blocking antibodies, was not obtained until 1944 when larger quantities of potent human anti-Rh serum became available for these tests.

In the test, a drop of the patient's serum is first mixed with a drop of a suspension of group O Rh-positive red cells and incubated in the water-bath. In the absence of Rh agglutinins, no clumping should be evident at this stage. Then a drop of anti-Rh agglutinating serum is added, and the mixture is reincubated in the water-bath. If the patient's serum does not contain any Rh antibodies, strong clumping should now be evident; on the other hand, if the patient's serum contains Rh blocking antibodies, the red cells will remain unagglutinated or the clumping will be distinctly weakened.

I have postulated that Rh blocking antibodies, in contrast to Rh agglutinins, are univalent. This would account for the ability of these antibodies to combine with Rh agglutinogen and to block the combining sites on the surface of the erythrocytes, but without clumping them. If this concept is correct, it seems reasonable to conclude that Rh blocking antibodies are comprised of smaller molecules than Rh agglutinins. Therefore, Rh blocking antibodies should be capable of traversing the placental barrier into the fetal circulation more readily and earlier in pregnancy than Rh agglutinins. This is supported by the clinical observation that the presence of Rh blocking antibodies is of more serious prognostic import than the presence of Rh agglutinins without blocking antibodies, e.g., when blocking antibodies are present stillbirths are more apt to result.

The discovery of the Rh blocking antibodies has also served to explain certain intragroup hemolytic transfusion reactions. In two such cases recently seen, the patients were Rh negative, but their sera contained no anti-Rh agglutinins, and in the usual compatibility test the sera of the patients failed to agglutinate the blood suspensions of the donors whose blood caused the reactions. However, the blocking tests were positive in both cases and showed the presence of Rh antibodies of high titer.

*Conglutination Test* (8). The discovery of the Rh blocking antibodies explains why the classic cross-matching tests have been inadequate to detect all cases of intragroup incompatibility. By slightly modifying the technic of the compatibility test, it is now possible to avoid this pitfall.

The new test for Rh sensitization, designated as the conglutination test, differs from the agglutination test in that it occurs in two stages instead of one and because a third component besides the Rh antigen and its specific antibody must be present in the mixture in order for clumping to occur. The third component, like complement in serologic hemolysis, is absorbed onto the specifically sensitized red cells and then causes them to stick together. However, this third component is distinct from complement. It resists heating at 60° C. and is a colloidal constituent (conglutinin) in the plasma probably identical with the so-called X-protein, which is a large molecular complex of albumin, globulin and phospholipid. The Rh antibody participating in the conglutination reaction is univalent and is best referred to as Rh glutinin, with the understanding that it is still uncertain whether or not glutinin is identical with blocking antibody.

The difference between Rh agglutination and Rh conglutination can be summarized as follows:

Rh-positive red cells + anti-Rh agglutinins forms Agglutination;

Rh-positive red cells + anti-Rh glutinins + X-protein forms Conglutination.

While X-protein or conglutinin is heat-stable it has the peculiarity that it dissociates readily into its constituent smaller molecules of albumin and globulin, upon slight dilution of the plasma with water. This explains why conglutination does not occur under the conditions existing in the agglutination test, because the use of saline in preparing the red blood cell suspensions and for diluting the patient's serum is sufficient to partly or completely dissociate the X-protein. The conglutination test is therefore carried out like the agglutination test except that the use of saline or any crystalline

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solution strictly is avoided. The red cells are suspended in the individual's own plasma or serum, or more conveniently in inactivated group AB serum. The patient's serum is tested undiluted, or in titrations, the serum is diluted with group AB serum instead of saline solution. I believe that the slide test of Diamond and Abelson (10), and the capillary tube test of Chown (11), when properly carried out, depend for their success on a conglutination reaction rather than on an agglutination reaction as originally stated by these workers.

In tests for Rh sensitization by the conglutination technic, positive reactions will be obtained in all cases where the patient's serum contains Rh agglutinins or Rh blocking antibodies or both, and occasionally when the other two tests are negative or inconclusive. The conglutination test is the most reliable indication of the presence or absence of Rh sensitization because it is always or almost always positive if the patient is sensitized (9, 12). Moreover, glutinin is univalent and therefore presumably comprised of small molecules, so this antibody, like blocking antibody, plays a more important rôle than Rh agglutinin in the pathogenesis of congenital hemolytic disease.

The bizarre behavior of congenital hemolytic disease, so that some infants do not present signs of hemolysis until several hours or days after birth, can probably be attributed to conglutinin or X-protein, the third component necessary for *in vitro* conglutination, and therefore probably important for *in vivo* hemolysis.[1] Perhaps in these cases X-protein does not form until after birth, at which time the profound physiological changes occurring bring about aggregation of serum proteins into more complex molecules. In this connection, Pedersen has found that serum from cow's fetus and newborn calves and foals contains large amounts of a special globulin of low molecular weight, designated fetuin by him, which he believes to be one of the precursors of X-protein. Fetuin has also been found in human umbilical cord serum, though in smaller amount.

*Other Tests for Rh Sensitization.* Coombs, Mourant and Race (13) have recently described a new and ingenious method of detecting univalent Rh antibodies (blocking antibodies or glutinins). The principle of this test is that Rh-positive red cells treated with human serum containing univalent Rh antibodies become coated with antibody globulin. If such sensitized cells are now tested with anti-human globulin precipitin serum they should agglutinate. In fact, this technique did prove to be a sensitive and specific test for Rh sensitization. It was found, moreover, that ordinary anti-human serum precipitins gave as satisfactory results as anti-globulin precipitins. The following precautions must be observed when carrying out the test. (1) The red cells after being treated with the patient's serum must be washed three times with saline solution in order to remove all traces of human serum from the supernatant, which might inhibit the reaction. (2) The precipitin serum used for the tests must first be absorbed with packed, washed, pooled human red cells of groups O, A and B to remove heteroagglutinins for human red cells. Then the serum must be standardized by titrating it against washed human Rh-positive red cells that have been sensitized with univalent Rh antibody. For the tests, a dilution of the precipitin serum is used which gives sharp and specific agglutination, e.g., 1:20.

The various tests for Rh sensitization that have been described are readily adapted for use as compatibility tests before blood transfusions, by merely substituting the prospective donor's blood for the known Rh-positive blood in tests with the patient's serum. Obviously, the tests will serve to detect incompatibility due to other blood factors as well as Rh. As compatibility tests, the most useful of the methods mentioned are the ordinary agglutination tests and Diamond and Abelson's slide test. In the latter, a small drop of the patient's oxalated plasma is mixed with a large drop of the prospective donor's whole oxalated blood on a glass slide and the reactions are read within 5 to 10 minutes. This test is somewhat more sensitive if the slide is placed on a special warm stage like the one devised by Diamond and Abelson (10).

The final proof of compatibility of a prospective donor's blood is the result of the biological test. Wiener's biological test (14, 15) is useful in cases where Rh sensitization may be present, but there isn't time or facilities for carrying out the *in vitro* tests. The biological test should also be carried out in all cases where the *in vitro* tests are at all equivocal, or if there is the slightest doubt as to the prospective donor's compatability. Thus, the biological test supplements but does not supplant the *in vitro* tests. In the biological test, 50 cc. of the

[1] Probably complement also plays a rôle in the reactions.

prospective donor's blood are injected into the patient by syringe, or are diluted with saline solution and administered by the gravity method. If no clinical symptoms and no darkening in the color of the patient's plasma occur within one or two hours after the injection of the test dose of 50 cc. of blood, the patient can be given any quantity of blood from this donor without danger.

### Rh Blood Types[2]

Before proceeding with the presentation of illustrative clinical material, a brief description of the Rh blood types is in order.

While our anti-rhesus immune guinea-pig or rabbit sera all gave parallel reactions, agglutinating the blood of approximately 85 per cent of all white individuals (3), we soon found that human antisera from Rh-negative patients sensitized to the Rh factor varied in their specificities (4). The great majority of the human antisera gave reactions identical with those of the anti-rhesus sera, and such human antisera are now designated as standard anti-Rh or anti-$Rh_0$. The differences among human antisera were soon explained by the demonstration of two additional varieties of Rh agglutinins, one giving 70 per cent positive reactions and designated as anti-Rh′, the other giving 30 per cent positive reactions and designated anti-Rh″. If blood specimens are tested with all three antisera, anti-$Rh_0$, anti-Rh′ and anti-Rh″, eight distinct types of human blood can be identified instead of the two, Rh positive and Rh negative, detected with the aid of standard human anti-Rh serum or animal anti-rhesus serum alone. As Wiener (16, 17) has shown, the three Rh antisera detect three corresponding Rh factors, $Rh_0$, Rh′ and Rh″, which in combination give rise to at least five Rh agglutinogens instead of one, namely $Rh_0$, Rh′, Rh″, $Rh_1$ (or $Rh_0$) and $Rh_2$ (or $Rh_0''$). These five agglutinogens in combination determine the eight Rh types, which are hereditarily transmitted by means of at least six allelic genes, *$Rh_0$*, *Rh′*, *Rh″*, *$Rh_1$*, *$Rh_2$*, and *rh*.

Anyone familiar with the serology and genetics of the four Landsteiner blood groups can readily master the eight Rh blood types. First, considering only the reactions of anti-Rh′ and anti-Rh″, these two antisera determine four types of blood entirely analogous serologically and genetically to the four blood groups. If, in addition, the reactions with anti-$Rh_0$ serum are taken into account, eight types of blood result as shown in table 1.

TABLE 1

The Eight Rh Blood Types*

| Bloods containing $Rh_0$ | | | | Bloods lacking $Rh_0$ | | | |
|---|---|---|---|---|---|---|---|
| Designations of types | Reactions with sera | | | Designations of types | Reactions with sera | | |
| | Anti-Rh′ | Anti-Rh″ | Anti-$Rh_0$ | | Anti-Rh′ | Anti-Rh″ | Anti-$Rh_0$ |
| $Rh_0$ | − | − | + | Rh- | − | − | − |
| $Rh_1(Rh_0')$ | + | − | + | Rh′ | + | − | − |
| $Rh_2(Rh_0'')$ | − | + | + | Rh″ | − | + | − |
| $Rh_1Rh_2(Rh_0'Rh_0'')$ | + | + | + | Rh′ Rh″ | + | + | − |

* Wiener, A. S.: Amer. J. Clin. Path., 15: 106, 1945.

The types are named after the antisera with which they react (17). For example, type $Rh_0$ reacts with anti-$Rh_0$, but not with anti-Rh′ or anti-Rh″; similarly, type Rh′, reacts with anti-Rh′, but not with anti-$Rh_0$ or anti-Rh″, etc. Blood reacting with anti-Rh′ and anti-$Rh_0$ but not with anti-Rh″ is designated $Rh_1$ (short for $Rh_0'$) instead of $Rh_0Rh'$ because the factors $Rh_0$ and Rh′ in such blood are ordinarily hereditarily transmitted as a unit, like the agglutinogens $A_1$ and A in blood of subgroup $A_1$ rather than like the agglutinogens A and B in group AB blood. Thus, in the mating Rh- × $Rh_1$, as a rule, either the children are all type $Rh_1$, or half belong to type $Rh_1$ while the remainder are Rh negative. To be sure, the factors $Rh_0$ and Rh′ will segregate in occasional matings involving type $Rh_1$ individuals, namely, when the type $Rh_1$ parent belongs to genotype *$Rh_0Rh'$*, but such cases are rare and have not been encountered yet because of the low frequencies of genes *$Rh_0$* and *Rh′*. For the

[2] For a detailed discussion of the Rh blood types, *see:* Wiener, A. S., and Sonn, E. B.: The Rh Series of Allelic Genes, with Special Reference to Nomenclature. Bull. N. Y. Acad. Sci., in press.

same reason, blood reacting with anti-Rh″ and anti-$Rh_0$ but not with anti-Rh′ is designated as type $Rh_2$ (or $Rh_0''$) rather than $Rh_0Rh''$. On the other hand, types Rh′Rh″ and $Rh_1Rh_2$ are so designated because, with rare exceptions, such bloods contain two separate agglutinogens.

The Rh blood types, like the blood groups and M-N types, exhibit striking differences in distribution in various races and promise to have important applications in anthropology (18). Some of the findings on the racial distribution of the Rh blood types are summarized in table 2. Chinese, Japanese, American Indians, Filipinos, Hawaiians and Australian aborigines are characterized by the virtual absence of the Rh-negative type; in negroes, the most striking finding is the high incidence of type $Rh_0$, which is about 20 times as frequent as in whites. A very pretty case is that of the white Porto-Ricans, where the Rh types clearly indicate the presence of an unnoticed negro admixture. Some correlation between the frequency of the Rh-negative type in the population and the incidence of congenital hemolytic disease is to be expected, and it is of interest to note that Levine and Wong report that this disease is virtually unknown among Chinese.

The theory of six allelic genes has been tested by studying the Rh blood types in families, and by the gene frequency method, and the findings support the theory in its essential details (19). In table 3 are presented our findings on the heredity of the Rh blood types in 197 families with 463 children. Only two apparent contradictions to the genetic theory were encountered and both of these proved to be due to illegitimacy. In the statistical test by the gene frequency method, the findings on white individuals have been in good agreement with the theory of six allelic genes. In American Indians and Mongolians, however, the calculated sum of the gene frequencies falls short of 100 per cent, and this we attribute to the occurrence in these peoples of an exceptionally high frequency of the rare genes $Rh_y$ and/or $Rh_z$ of Race and Taylor (20). Negroes are characterized by an exceptionally high percentage of individuals with blood giving weak or intermediate reactions with one or

TABLE 2

Distribution of the Rh Blood Types

| Population tests | Number of persons tested | Frequencies of Rh types (per cent) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Rh- | $Rh_1$ | $Rh_2$ | $Rh_1Rh_2$ | $Rh_0$ | Rh′ | Rh″ | Rh′Rh″ |
| Whites, N. Y. C. [a] | 1000 | 12.9 | 54.1 | 12.8 | 16.4 | 2.6 | 0.9 | 0.3 | 0 |
| Whites, N. Y. C. [b] | 818 | 13.5 | 55.6 | 15.8 | 12.0 | 1.7 | 1.1 | 0.3 | 0 |
| Whites, N. Y. C. [c] | 2438 | 14.5 | 52.5 | 15.7 | 13.1 | 2.4 | 1.1 | 0.7 | 0.02 |
| Whites, Australia[d] | 350 | 14.9 | 54.0 | 12.6 | 16.5 | 0.6 | 0.9 | 0.5 | 0 |
| Negroes, N. Y. C.[e] | 223 | 8.1 | 20.2 | 22.4 | 5.4 | 41.2 | 2.7 | 0 | 0 |
| Asiatic Indians[f] | 156 | 7.1 | 70.5 | 5.1 | 12.8 | 1.9 | 2.6 | 0 | 0 |
| Chinese[g] | 132 | 1.5 | 60.6 | 3.0 | 34.1 | 0.9 | 0 | 0 | 0 |
| Mexican Indians[h] | 98 | 0 | 48.0 | 9.2 | 41.8 | 1.0 | 0 | 0 | 0 |
| Japanese [i] | 150 | 1.3 | 37.4 | 13.3 | 47.3 | 0 | 0 | 0 | 0.7 |
| Japanese [j] | 180 | 0.6 | 51.7 | 8.3 | 39.4 | 0 | 0 | 0 | 0 |
| Filipinos[d] | 100 | 0 | 87.0 | 2.0 | 11.0 | 0 | 0 | 0 | 0 |
| Indonesians[d] | 100 | 0 | 75 | 2 | 22 | 0 | 0 | 0 | 1 |
| White Porto-Ricans[k] | 179 | 10.1 | 39.1 | 19.6 | 14.0 | 15.1 | 1.7 | 0.5 | 0 |

[a] Old Series: Wiener, A. S.: Amer. J. Clin. Path., 15: 106, 1945.
[b] New Series; Wiener, A. S., and Sonn, E. B.: Bull. N. Y. Acad. Sci., in press.
[c] Unger, L. J.: Personal communication.
[d] Simmons, R. T.: Personal communication.
[e] Wiener, Belkin and Sonn: Amer. J. Phys. Anthrop. N.S., 2: 187, 1944.
[f] Wiener, Sonn and Belkin: J. Immunol., 50: 341, 1945.
[g] Wiener, Sonn and Yi: Amer. J. Phys. Anthrop. N.S., 2: 267, 1944.
[h] Wiener, Zepeda, Sonn and Polivka: J. Exp. Med., 81: 559, 1945.
[i] Waller, R. K., and Levine, P.: Science, 100: 453, 1944.
[j] Miller and Taguchi: J. Immunol. 51: 227, 1945.
[k] Torregrosa, M. Vicente: Personal communication.

more of the Rh antisera, and this has been attributed to the existence of still more genes in the Rh allelic genes (21), the so-called "intermediate genes." For practical purposes, the theory of six allelic genes has proved adequate, because the genes *Rh*$_y$ and/or *Rh*$_z$ and the intermediate genes are quite rare among white individuals. Under the theory of six allelic genes, 21 genotypes are possible, and the genotype corresponding to each of the eight Rh blood types is readily ascertained as shown in table 4. If the genes *Rh*$_y$ and/or *Rh*$_z$ and the intermediate genes are taken into account, the situation naturally becomes far more complicated.

TABLE 3

SUMMARY OF AUTHOR'S FAMILY STUDIES ON THE Rh BLOOD TYPES*

| Mating | Number of families | Number of children of types | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Rh- | $Rh_1$ | $Rh_2$ | $Rh_1Rh_2$ | $Rh_0$ | Rh′ | Rh″ | Totals |
| Neg. × Neg. | 4 | 14 | 0 | 0 | 0 | 0 | 0 | 0 | 14 |
| Neg. × $Rh_1$ | 49 | 25 | 73 | 0 | 0 | 7 | 0 | 0 | 105 |
| Neg. × $Rh_2$ | 16 | 10 | 0 | 20 | 0 | 0 | 0 | 0 | 30 |
| Neg. × $Rh_1Rh_2$ | 15 | (1) | 18 | 14 | 0 | 0 | 0 | 0 | 33 |
| Neg. × $Rh_0$ | 3 | 3 | 0 | 0 | 0 | 3 | 0 | 0 | 6 |
| Neg. × Rh′ | 2 | 1 | 0 | (1) | 0 | 0 | 1 | 0 | 3 |
| Neg. × Rh″ | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 5 | 6 |
| $Rh_1$ × $Rh_1$ | 26 | 5 | 62 | 0 | 0 | 4 | 1 | 0 | 72 |
| $Rh_1$ × $Rh_2$ | 21 | 6 | 15 | 7 | 18 | 0 | 2 | 0 | 48 |
| $Rh_1$ × $Rh_1Rh_2$ | 27 | 0 | 46 | 8 | 25 | 0 | 0 | 0 | 79 |
| $Rh_1$ × $Rh_0$ | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| $Rh_1$ × Rh′ | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 3 |
| $Rh_1$ × Rh″ | 4 | 1 | 2 | 0 | 3 | 0 | 0 | 0 | 6 |
| $Rh_2$ × $Rh_2$ | 2 | 1 | 0 | 4 | 0 | 0 | 0 | 0 | 5 |
| $Rh_2$ × $Rh_1Rh_2$ | 6 | 0 | 2 | 8 | 8 | 0 | 0 | 0 | 18 |
| $Rh_2$ × $Rh_0$ | 2 | 0 | 0 | 1 | 0 | 4 | 0 | 0 | 5 |
| $Rh_1Rh_2$ × $Rh_1Rh_2$ | 10 | 0 | 3 | 1 | 17 | 0 | 0 | 0 | 21 |
| $Rh_1Rh_2$ × $Rh_0$ | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 2 |
| $Rh_1Rh_2$ × Rh′ | 2 | 0 | 1 | 1 | 2 | 0 | 0 | 0 | 4 |
| $Rh_0$ × Rh′ | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 2 |
| Totals | 197 | 69 | 226 | 66 | 73 | 19 | 5 | 5 | 463 |

* Wiener and Sonn: J. Lab. and Clin. Med., 30: 395, 1945.

TABLE 4

THE EIGHT Rh TYPES AND THEIR GENOTYPES

| Rh Types | Genotypes |
|---|---|
| Neg. | *rhrh* |
| Rh′ | *Rh′Rh′* and *Rh′rh* |
| Rh″ | *Rh″Rh″* and *Rh″rh* |
| Rh′Rh″ | *Rh′Rh″* |
| $Rh_0$ | $Rh_0Rh_0$ and $Rh_0rh$ |
| $Rh_1(Rh_0')$ | $Rh_1Rh_1$, $Rh_1rh$, $Rh_1Rh'$, $Rh_1Rh_0$, and $Rh'Rh_0$ |
| $Rh_2(Rh_0'')$ | $Rh_2Rh_2$, $Rh_2rh$, $Rh_2Rh''$, $Rh_2Rh_0$, and $Rh''Rh_0$ |
| $Rh_1Rh_2(Rh_0'Rh_0'')$ | $Rh_1Rh_2$, $Rh_1Rh''$, and $Rh'Rh_2$ |

### THE Hr FACTOR

The literature on the Hr factor is somewhat confused, because the early work was done with weak antisera, so that some of the findings were inaccurate and misleading. Levine and Javert (6) first reported that they had detected in the serum of an Rh-positive mother of an erythroblastotic infant an antibody which had the property of agglutinating all Rh-negative bloods. Because of this property of the serum, the new agglutinable property detected by it was designated as Hr, and the corresponding agglutinin as anti-Hr. Levine reported that his anti-Hr serum gave about 30 per cent positive reactions, and that all Rh-positive bloods not agglutinated by anti-Rh′ reacted with anti-Hr. On this basis he postulated that Hr and Rh were

allelic, without further clarifying his hypothesis. He also asserted that Hr incompatibility must be shown, the latter two statements have been contradicted by subsequent findings.

TABLE 5

THE REACTIONS DETERMINED BY THE SIX STANDARD GENES AND THE RARE GENES $Rh_y$ AND $Rh_z$

| Genes | Reactions with Rh Sera | | | Reactions with Hr Antiserum |
|---|---|---|---|---|
| | Anti-Rh′ | Anti-Rh″ | Anti-$Rh_0$ | |
| *rh* | Neg. | Neg. | Neg. | Pos. |
| $Rh_0$ | Neg. | Neg. | Pos. | Pos. |
| *Rh′* | Pos. | Neg. | Neg. | Neg. |
| $Rh_1$ | Pos. | Neg. | Pos. | Neg. |
| *Rh″* | Neg. | Pos. | Neg. | Pos. |
| $Rh_2$ | Neg. | Pos. | Pos. | Pos. |
| $Rh_y$ | Pos. | Pos. | Neg. | Neg. |
| $Rh_z$ | Pos. | Pos. | Pos. | Neg. |

In 1943, Race and Taylor (22) also detected in the serum of an Rh-positive mother of any erythroblastotic infant an agglutinin which reacted with all Rh-negative bloods, but differed from Levine and Javert's in that it gave 80 per cent positive reactions. As has been pointed out by Wiener et al. (23), however, Race and Taylor's serum detected the same blood property as Levine and Javert's serum, the lower percentage of positive reactions obtained by Levine being due to the use of a weaker antiserum which missed bloods heterozygous for the Hr factor. In this lecture, therefore, the blood property studied by the British investigators will also be designated as Hr. As postulated by Race et al. (24), Hr is a blood factor present in the agglutinogens determined by genes

TABLE 6

RELATION OF THE Hr FACTOR TO THE Rh BLOOD TYPES

| Rh Blood Type | Reactions with Rh Sera | | | Genotypes | Reactions with Hr antiserum* | Per cent observed (350 tests on white individuals N. Y. C.) |
|---|---|---|---|---|---|---|
| | Anti-Rh′ | Anti-Rh″ | Anti-$Rh_0$ | | | |
| Rh- | Neg. | Neg. | Neg. | *rhrh* | Strong | 12.3 |
| Rh′ | Pos. | Neg. | Neg. | *Rh′Rh′* | Neg. | 0 |
| | | | | *Rh′rh* | Weak | 1.1 |
| Rh″ | Neg. | Pos. | Neg. | *Rh″Rh″*<br>*Rh″rh* | Strong | 0.9 |
| Rh′Rh″‡ | Pos. | Pos. | Neg. | *Rh′Rh″* | Weak | 0 |
| $Rh_0$ | Neg. | Neg. | Pos. | $Rh_0Rh_0$<br>$Rh_0rh$ | Strong | 1.1 |
| | | | | $Rh_1Rh_1$<br>$Rh_1Rh'$ | Neg. | 19.7 |
| $Rh_1$ | Pos. | Neg. | Pos. | $Rh_1rh$<br>$Rh_1Rh_0$<br>$Rh'Rh_0$ | Weak | 36.9 |
| | | | | $Rh_2Rh_2$<br>$Rh_2Rh''$<br>$Rh_2rh$<br>$Rh_2Rh_0$<br>$Rh''Rh_0$ | Strong | 16.0† |
| $Rh_1Rh_2$‡ | Pos. | Pos. | Pos. | $Rh_1Rh_2$<br>$Rh_1Rh''$<br>$Rh'Rh_2$ | Weak | 11.7 |
| | | | | $Rh_1Rh_z$ | Neg. | 0.3 |

* Theoretically expected reactions. Actually the Hr antiserum used was of such high titer that all positive bloods gave uniformly strong reactions.

† Includes one blood giving intermediate reactions (Rh.).

‡ If the existence of both genes $Rh_y$ and $Rh_z$ is admitted, then there are 19 genotypes possible in these types instead of four as given in table 4. The additional 15 genotypes—if all of them actually exist—must be quite rare, so for simplicity only the most common, genotype $Rh_1Rh_z$, is given in the table.

considered as a possibility whenever an Rh-positive mother has an Rh-negative child, and that all type $Rh_1Rh_2$ individuals are Hr-negative. As will be

*Rh*$_2$, *Rh″*, $Rh_0$ and *rh*, but absent from the agglutinogens determined by genes $Rh_1$, and *Rh′* (and $Rh_y$ and $Rh_z$). From the reactions determined by

the six genes (table 5), the reactions of the 21 genotypes are readily ascertained as shown in table 6. In giving the expected reactions with anti-Hr serum, it is postulated that a single dose of a gene positive for Hr determines a weaker reaction with anti-Hr than a double dose of Hr-positive genes (22, 23). (This idea is supported by observations made in tests with weak anti-Hr serum, while in tests with potent Hr antisera it is difficult or impossible to demonstrate the gene-dose effect.) It will be seen that the expected percentage of positive reactions, approximately 80 per cent, closely agrees with that reported by Race and Taylor, and that observed by the speaker. If only the strong reactions are counted, then the percentage or positive reactions becomes 30 per cent, as reported by Levine. This explains the apparent contradiction between the reports of Levine, and Race and Taylor, and why Levine thought that type $Rh_1Rh_2$ bloods were Hr negative. Since Hr-negative mothers can only belong to genotype $Rh_1Rh_1$, $Rh_1Rh'$ or $Rh'Rh'$, they must transmit either an $Rh_1$ or an $Rh'$ gene to every child, and so cannot have any Rh-negative children, contrary to the assertion made by Levine.

The main clinical application of the Hr factor is as presumptive test for homo-/or heterozygosity of type $Rh_1$ fathers in families with erythroblastotic infants (22). The diagnosis is only *presumptive* because there are five genotypes in type $Rh_1$, while anti-Hr serum merely subdivides type $Rh_1$ into two parts (23). Hr-negative individuals of type $Rh_1$ are almost surely homozygous for $Rh_1$, while Hr-positive individuals of type $Rh_1$ are almost always heterozygous and bear gene *rh*.

The accuracy of the theory of Race et al. regarding the Hr factor has been confirmed by family studies (25) and by the gene frequency method (26). Since every gene negative for factor Rh′ is positive for factor Hr, it is evident that factors Rh′ and Hr are related to each other serologically and genetically like M and N. To indicate this the standard Hr factor which we have described is perhaps better known as Hr′ and the corresponding serum as anti-Hr′. Of the other two Hr factors postulated by Fisher (27), Hr″ has recently been found by Mourant (28), while convincing evidence is still lacking (26) concerning the existence of $Hr_0$.

### Clinical Application (15, 29, 30)

A few cases will now be described which illustrate the application of the Rh blood types in relation to the diagnosis, treatment and prognosis of congenital hemolytic disease.

*Case 1.* I was requested by Dr. J. Hoffman, at the Israel Zion Hospital, to see an intensely jaundiced infant, two months of age, in order to determine whether it was suffering from congenital stricture of bile ducts or congenital hemolytic disease.

The mother of the patient gave the following obstetrical history: The first pregnancy terminated at term, in 1935, with a normal female child. The second pregnancy, in 1939, yielded a male infant who developed anemia after birth; but recovered following transfusion therapy. The third pregnancy, in 1945, resulted in the patient who shortly after birth, developed jaundice and anemia for which he was treated by transfusions of Rh-negative blood. The anemia improved, but deep jaundice persisted.

The patient's mother had never received a blood transfusion. The grouping and Rh tests gave the following results:

| *Blood of* | *Groups and Sub-groups* | *MN Type* | *Rh Type* | *Hr Reaction* |
|---|---|---|---|---|
| Father | O | M | $Rh_2$ | Positive |
| Mother | $A_2$ | MN | Neg. | Positive |
| 10 yr. old sister | O | MN | $Rh_2$ | Positive |
| 6 year old brother | $A_2$ | MN | $Rh_0$ | Positive |
| Patient | O | MN | $Rh_2$ | Positive |

The fact that the mother was Rh negative, while the father and all three children were Rh positive, could, of course, be merely coincidental. However, in the maternal serum anti-$Rh_0$ agglutinins of titer 16 were detected demonstrating that she was sensitized to the Rh factor, and establishing the diagnosis of congenital hemolytic disease.

The case is typical in that it demonstrates how the first Rh-positive infant escapes the disease, while the subsequent infants are affected progressively more severely as the sensitization of the mother increases in degree with each pregnancy. The second infant recovered fully even though the donors whose blood was used for the transfusions were not selected with regard to the Rh factor, then unknown. The patient was treated properly with transfusions of Rh-negative blood and nevertheless had an unusual complication in that damage to the liver finally caused death at the age of three months.

The Hr factor is of no assistance in determining the hetero-/or homozygosity of the father in this case, because he does not belong to type $Rh_1$ but to type $Rh_2$. However, the fact that he has had children of types $Rh_2$ and $Rh_0$ proves that he be-

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longs to genotype $Rh_2Rh_0$. Therefore, every future child of this couple must be Rh positive, either type $Rh_2$ or $Rh_0$, and would be certain to have congenital hemolytic disease.

*Case 2.* This patient was referred by Dr. B. Merriam with the history that she was in the eighth month of pregnancy and that the fetal heart sounds had not been audible for the past three weeks. This was the patient's third pregnancy. The first pregnancy had terminated with a normal female child now four years old, while the second had yielded a seven-month macerated fetus.

Tests on the patient, her husband and the daughter showed the following:

| *Blood of* | *Group and Sub-group* | *MN Type* | *Rh Type* | *Hr Reaction* |
|---|---|---|---|---|
| Husband | O | MN | $Rh_1$ | Negative |
| Patient | $A_2$ | M | Neg. | Positive |
| Daughter | $A_2$ | M | $Rh_1$ | Positive |

No Rh agglutinins were demonstrable in the patient's serum, but Rh blocking antibodies were present in low titer (2 units). By the conglutination technic Rh antibodies were readily demonstrable in the patient's serum in dilutions as high as 1 to 50. These findings therefore established the diagnosis of congenital hemolytic disease as the cause of the stillbirth after the second pregnancy and the intrauterine death during the present pregnancy.

Shortly after these tests were carried out the patient gave birth to a macerated fetus, after which she had a hemorrhage which was treated by plasma transfusions. The patient probably owes her life to the newer knowledge of the Rh blood factors and the blocking antibodies. Under similar circumstances before the discovery of the Rh factor, the patient would have been treated by transfusions of whole blood from an unselected and therefore probably Rh-positive, group A donor, because blocking antibodies are not detectable in the usual cross-matching tests.

The more severe manifestations of congenital hemolytic disease in this case, as contrasted with case 1, are in line with the remarks concerning the more serious prognostic significance of Rh blocking antibodies as compared with Rh agglutinins. Moreover, the husband of the patient is Hr negative so that the prognosis for further pregnancies for this couple is practically hopeless, because every future pregnancy would be expected to yield an Rh-positive fetus and therefore terminate with stillbirth. In case 1, on the other hand, where the degree of Rh sensitization of the mother is not as pronounced, future children, though certain to be affected with congenital hemolytic disease, might nevertheless prove viable and recover after transfusion therapy.

*Case 3.* This case was referred to me by Dr. I. Frohman, who is reporting it in detail elsewhere. The patient was first admitted to the Rockaway Beach Hospital during the sixth month of her eleventh pregnancy because of an abruptio placentae. She was delivered shortly afterward of a stillborn fetus with hydrops.

The obstetrical history, and the results of grouping and Rh tests are as follows:

| *Blood of* | *Group* | *MN Type* | *Rh Type* |
|---|---|---|---|
| Husband | O | MN | $Rh_2$ |
| Patient | O | N | Neg. |
| *Pregnancies:* | | | |
| 1. 1928. Normal male child. | O | MN | $Rh_2$ |
| 2. 1929. Normal male child. | O | MN | $Rh_2$ |
| 3. 1930. Premature stillbirth at 6½ months. Patient had hypertension during pregnancy. | | | |
| 4. 1932. Normal male child. | O | N | Neg. |
| 5. 1935. Female child. Jaundice on 8th day; cleared in a few days. | O | N | $Rh_2$ |
| 6. 1936. Normal male child. | O | MN | Neg. |
| 7. 1938. Stillborn male child. | | | |
| 8. 1938. Fraternal twins in separate sacs. Male twin normal. Female twin died after 13 hrs. from icterus gravis and hydrops. | O | MN | Neg. |
| 9. 1940. Normal male child | O | N | Neg. |
| 10. 1943. Normal male child | O | N | Neg. |
| 11. 1944. Stillbirth; present pregnancy. | | | |

No anti-Rh agglutinins were demonstrable in the patient's serum, but Rh blocking antibodies were present in low titer (2 units). These findings

therefore indicate that the stillbirths that this patient had after the fifth pregnancy were due to congenital hemolytic disease. The stillbirth occurring at the third pregnancy must be attributed to some mechanism other than isoimmunization in pregnancy.

The husband of this patient, in contrast to the fathers in cases 1 and 2, is heterozygous for the Rh factor and belongs to genotype $Rh_2rh$. It would therefore be expected that half of the children from this couple should be Rh positive (type $Rh_2$) and half, Rh negative. If the stillbirths are counted as Rh positive, a close approximation is obtained to the expected 1:1 ratio. In future pregnancies, this couple has a 50 per cent chance of having an Rh-negative and therefore normal child. Should such a fetus be Rh positive, it almost surely would be stillborn.

In this case it took more than one pregnancy with Rh-positive fetuses to sensitize the mother sufficiently to give rise to infants with hemolytic disease. Nevertheless, the sensitization, when it finally did develop, was intense, as evidenced by the presence of blocking antibodies in the maternal serum and the occurrence of stillbirths in the 7th, 8th and 11th pregnancies. The mild jaundice exhibited by the female child born after the 5th pregnancy was probably a manifestation of a very mild hemolytic disease. After the fifth pregnancy the sensitization became more pronounced so that only Rh-negative infants survived.

Of particular interest is the eighth pregnancy which yielded a pair of unlike sexed twins. The male twin was Rh negative and normal while the female twin died within 13 hours from icterus gravis, undoubtedly because she was Rh positive.

*Case 4.* The patient was a male infant, 6 days of age, from the service of Dr. David A. Meyers, at the Adelphi Hospital. The infant was the eighth born to his parents. The first seven had been all normal at birth, and all were alive except the oldest, who had died following an automobile accident. On the second day of life the patient was noticed to be jaundiced. The jaundice deepened and by the fifth day the hemoglobin concentration had dropped to 63 per cent, the red cell count was 2.9 million, and the blood smear showed 5 nomoblasts per 100 w.b.c.

Blood tests on the parents and children showed the following:

| *Blood of* | *Group* | *MN Type* | *Rh Type* | *Hr Reaction* |
|---|---|---|---|---|
| Father | O | M | $Rh_1$ | Negative |
| Mother | O | M | Neg. | Positive |
| 1. Brother born 1931. (Not alive.) | | | | |
| 2. Sister born 1933. | O | M | $Rh_1$ | Positive |
| 3. Sister born 1938. | O | M | $Rh_1$ | Positive |
| 4. Sister born 1939. | O | M | $Rh_1$ | Positive |
| 5. Sister born 1941. | O | M | $Rh_1$ | Positive |
| 6. Brother born 1942 | O | M | $Rh_1$ | Positive |
| 7. Sister born 1943. | O | M | $Rh_1$ | Positive |
| 8. Patient | O | M | $Rh_1$ | Positive |

The maternal serum contained no detectable Rh agglutinins and gave only a questionable blocking reaction, but by the conglutination method Rh antibodies of titer 16 were readily demonstrable, proving that the patient's mother was sensitized to the Rh factor and establishing the diagnosis of congenital hemolytic disease. By the conglutination technique Rh antibodies were also readily detected in the infant's plasma, and autoagglutination of the infants' red cells by his own plasma was demonstrable. This corroborates my remarks concerning the ease with which maternal univalent antibodies (glutinins) pass through the placental barrier into the fetal circulation.

A remarkable feature of this case is the large number of pregnancies required to induce Rh sensitization, despite the fact that every child was Rh positive. There is no doubt that the father is hemozygous (genotype $Rh_1Rh_1$) because he is Hr negative and every one of the seven children tested belongs to type $Rh_1$. Therefore, if this couple has any more children, such children are certain to have congenital hemolytic disease.

For treating the infant, 200 cc. of blood were obtained from a group O, Rh-negative professional donor. Half of the blood was transfused at once, the remainder on the following day. The infant improved immediately, the jaundice cleared, and when the patient was seen a week later the hemoglobin was 85 per cent. The patient was discharged from the hospital, and the parents were instructed to return with the patient in a week. The patient was not brought back until it was five weeks old, however, and by that time the hemoglobin had dropped to 40 per cent. Two hundred cc. of blood were then drawn from the patient's mother, and the washed and packed red cells (about 80 cc.) transfused by syringe and two-way stopcock into a scalp vein. The hemoglobin rise

this time was sustained, and complete recovery followed.

The presence of Rh antibodies in the infant's serum, as demonstrated in this case and other cases, is the rationale for the use of Rh-negative blood when treating infants with hemolytic disease, even though the infants themselves are Rh positive. When Rh-negative donors are not available, it is convenient to transfuse the mother's washed cells, and if the packed red cells are transfused, it is possible to get the effect of a transfusion of twice the volume of whole blood. The use of maternal washed cells is permissible even though the mother's blood belongs to an incompatible blood group, and preliminary grouping, Rh and cross-matching tests may be dispensed with if facilities for carrying out the tests are not available. One must carefully control the amount of blood transfused, taking into account the infant's blood volume as well as the hemoglobin. The injection of too much blood has caused fatal polycythemia.

*Case 5.* A physician in Santiago, Chile, reported that his wife was in the sixth month of her third pregnancy and showed signs of hydramnios. He was concerned because he had found his wife to be Rh negative and himself Rh positive. He could not detect any Rh agglutinins in his wife's serum, but the patient gave the following significant obstetrical history:

The first pregnancy occurred in 1943. This took place three months after marriage when the patient had a ruptured ectopic gestation for which an operation was performed. After the operation she was given two transfusions of group A bank blood, not selected for the Rh factor. There were no untoward reactions following these transfusions.

The second pregnancy occurred in 1944 and terminated with an eight-month macerated fetus.

Grouping and Rh tests were carried out on blood samples mailed from Chile and gave the following results:

| *Blood of* | *Group and Sub-group* | *MN Types* | *Rh Types* | *Hr Reaction* |
|---|---|---|---|---|
| Husband | O | MN | $Rh_1$ | Negative |
| Patient | $A_2$ | MN | Neg. | Positive |

No Rh agglutinins could be detected in the patient's serum but blocking antibodies were present in high titer (50 units), and by the conglutination technique Rh antibodies of titer 90 were demonstrable. In view of the high titer of Rh blocking antibodies in the patient's serum, and the fact that her husband was Hr negative, the prognosis for the present pregnancy was grave. In fact, the pregnancy soon did terminate with a seven-month stillbirth.

There is no doubt that the two blood transfusions given to this patient were the cause of her sensitization to the Rh factor, because the ectopic pregnancy had not advanced far enough to sensitize her. Had Rh-negative blood been transfused, most likely the second pregnancy would have yielded a viable infant. This case serves to illustrate the importance of Rh tests before giving blood transfusions to women in the child-bearing age, as already pointed out.

*Case 6.* The patient was an infant who became pale and then jaundiced shortly after birth, so that blood transfusion therapy was necessary. The infant was the result of its mother's second pregnancy; the first pregnancy had terminated with a normal female child, now 4 years of age.

Grouping tests on the infant, his parents and sister gave the following results:

| *Blood of* | *Group* | *MN Type* | *Rh Type* | *Hr Reaction* |
|---|---|---|---|---|
| Father | O | MN | $Rh_2$ | Positive |
| Mother | O | M | $Rh_1Rh_2$ | Positive |
| Sister (4 yrs.) | O | MN | $Rh_2$ | Positive |
| Patient | O | M | $Rh_1$ | Positive |

The results came as a surprise, because we had felt reasonably certain from the clinical picture that the infant had congenital hemolytic disease. However, this diagnosis could now be excluded, especially because the maternal sera contained no abnormal isoantibodies.

The history was then obtained that the patient had had a traumatic delivery. He soon died, despite transfusion therapy, and an autopsy revealed the presence of a ruptured liver with hemorrhage into the parenchyma of the liver.

*Case 7.* This case was referred by Dr. A. M. Young of the Mount Sinai Hospital in Cleveland, Ohio, because the patient, a newborn infant, had all the clinical signs and symptoms of congenital hemolytic disease, yet mother and infant were both Rh positive. In the maternal serum an irregular agglutinin was detected, which I was requested to identify.

Grouping and Rh tests showed the following:

| *Blood of* | *Group and Subgroup* | *MN Type* | *Rh Type* |
|---|---|---|---|
| Mother | $A_1$ | MN | $Rh_1$ |
| Infant | $A_1$ | MN | $Rh_1Rh_2$ |

Thus, the infant's red blood cells contain all three Rh factors, $Rh_0$, Rh′ and Rh″, while the maternal red cells contain only factors $Rh_0$ and Rh′. The presence in the maternal serum of an atypical immune isoagglutinin of titer 32 was corroborated. As expected, this proved to correspond in specificity to anti-Rh″.

While type $Rh_1$ mothers with type $Rh_2$ or type $Rh_1Rh_2$ infants, and type $Rh_2$ mothers with type $Rh_1$ or type $Rh_1Rh_2$ infants are quite common, these combinations only rarely give rise to cases of congenital hemolytic disease, because factors Rh′ and Rh″ are much weaker antigens than $Rh_0$. As already mentioned, about 90 per cent of the clinical cases of congenital hemolytic disease can be traced to the $Rh_0$ factor.

*Case 8.* A 12-day old infant was seen in consultation with Dr. Benjamin A. Bloom, because of the sudden appearance of jaundice and pallor the day before. The patient was the first child. Her mother had never had a previous pregnancy and had never received a blood or plasma transfusion. The patient was born at term but her birth weight was only 4 pounds, 11 ounces. In all other respects she appeared normal and was discharged from the hospital on the eighth day. At home, she made satisfactory progress until jaundice and anemia appeared on the 11th day. Blood count performed on the twelfth day showed: Hgb. 50 per cent, R.B.C. 1.75 million, W.B.C. 17,000, Polys, 41, Lymphs 53, Monos 6, no nucleated red cells on smear.

Grouping and Rh test showed the following:

| *Blood of* | *Group and Sub-group* | *MN Type* | *Rh Type* | *Hr Reaction* |
|---|---|---|---|---|
| Father | $A_1$ | N | $Rh_0$ | Positive |
| Mother | O | MN | $Rh_1Rh_2$ | Positive |
| Patient | $A_1$ | N | $Rh_1$ | Positive |

Since the patient's mother belonged to type $Rh_1Rh_2$ and was Hr positive this excluded the Rh factors and the Hr factor as having any bearing on the problem. The incompatibility in blood groups suggested that this might have some bearing on the problem, so the isoagglutinin titers of the maternal serum were determined. By the agglutination method the titers were about 25 to 50 times as high as the average normal titer, namely, the anti-A titer (for $A_2$ test cells) was 500, while the anti-B titer was 250. By the conglutination technique the titers were even higher, namely, 5000 for anti-A and 500 for anti-B. In view of these findings there could be no doubt but that this patient's hemolytic anemia was due to isoimmunization of the mother against the agglutinogen A in the infant's blood.

Two of the questions raised by this case are how congenital hemolytic disease developed in a first born in the absence of previous sensitization of the mother by transfusion, and why the onset of the disease was delayed until the 11th day. Probably the high anti-A titer found in the tests did not accurately reflect the titer during pregnancy because, for reasons already pointed out, the isoantibody titer often rises after delivery. Since the infant had been breast-fed, she probably ingested larger and larger quantities of A antibodies as the maternal isoantibody titer rose, and finally enough antibody was absorbed by the infant to bring about hemolysis. This serves to emphasize the importance of interdicting breast feeding in all cases of congenital hemolytic disease. Another factor possibly delaying hemolysis was the infant's immaturity judging from its low weight, and the corresponding immaturity of her X-protein.

In another and milder case of congenital hemolytic disease in a first-born infant due to A-B isoimmunization, the mother gave the significant history that two years previously she had received two transfusions of reconstituted, desiccated pooled plasma. Experiments performed by me demonstrate that the intravenous injection of as little as 40 cc. of such plasma can induce a pronounced rise in titer of the isoagglutinins anti-A and anti-B. This suggests that plasma transfusions should not be given indiscriminately to women in the childbearing age, and it might also be mentioned that injections of therapeutic horse antisera may produce the same effect because such sera also contain A and B group substances. For the same reason the indiscriminate use of group O blood conditioned with A and B group substances for female patients of all groups may not be entirely unobjectionable.

Tests on the infant's saliva showed her to be a secretor, thus disproving the contention that only non-secretors are subject to congenital hemolytic disease due to A-B isoimmunization.

The infant was given a transfusion of 60 cc. of the packed, washed red cells of her mother. When the patient was seen three days later, her hemoglobin had risen to 66 per cent. By the end of the week, however, the hemoglobin had fallen to 45 per cent so a second transfusion of washed maternal

red cells was given. Again the hemoglobin rose, and this time the improvement was sustained.

*Case 9.* The following is a case which I studied in collaboration with Dr. Harry Bakwin.

The patient was a child, 2½ years of age, admitted to the Pediatric Wards at Bellevue Hospital because of athetosis and mental retardation. There was a history of severe illness at the fourth day of life. No other significant information was available except that the patient was suspected to have some sort of extrapyramidal brain lesion.

Grouping and Rh tests on the patient, his parents and older brother showed the following:

| *Blood of* | *Group and Subgroup* | *MN Type* | *Rh Type* |
|---|---|---|---|
| Father | $A_2$ | MN | $Rh_1$ |
| Mother | B | M | Neg. |
| Brother (4 yrs. old) | B | MN | $Rh_1$ |
| Patient | O | MN | $Rh_1$ |

Tests on the maternal serum showed the presence of anti-$Rh_0$ agglutinins of titer 5, proving that the patient's mother was sensitized to the Rh factor.

In view of these findings, it seems reasonable to conclude that the severe illness this patient had in infancy must have been congenital hemolytic disease. The patient's present signs of cerebral damage could then be explained as an after-effect of kernicterus, one of the fortunately uncommon sequelae of this disease.

## Conclusions

With the laboratory methods now available, it is possible to diagnose accurately practically every case of congenital hemolytic disease, or to exclude this diagnosis. It is also possible to specify more precisely the pathogenesis, whether due to isoimmunization to one or more of the Rh factors, $Rh_0$, Rh′ and Rh″, or to the Hr factors or the A-B-O factors.

The great majority of erythroblastotic infants born alive can be saved by transfusions of Rh-negative blood or washed maternal red cells. However, no effective method is known for saving infants from the lethal effects of certain hepatic injuries sustained as a result of the disease, or from kernicterus or hemorrhagic complications. The nature of the constitutional predisposition which makes one individual easier to sensitize to the Rh factor than another is not clearly understood.

Future work should be concerned primarily with the prophylaxis and treatment of congenital hemolytic disease. This problem will not be completely solved until effective methods have been devised for treating sensitized Rh-negative women, so that they are capable of bearing normal Rh-positive infants.

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## Résumé

Le diagnostic précis de l'ictère hémolytique congénital peut maintenant être affirmé ou infirmé dans la majeure partie des cas avec l'aide des procédés nouveaux du laboratoire. La pathogénie de cette maladie peut être exposée avec plus de précision; ou bien qu'elle soit due à l'iso-immunisation d'un seul ou de plusieurs des facteurs Rh; $Rh_0$, Rh′, Rh″; ou qu'elle soit due aux facteurs Hr ou aux facteurs A-B-O-.

La plupart des nouveaux-nés souffrant d'ictère hémolytique congénital peuvent être sauvés par des transfusions de sang à facteur Rh négatif, ou par la transfusion de globules rouges provenant du sang maternel, lesquels globules rouges auront été préalablement lavés. Cependant on ne connait pas encore de méthode adéquate pour combattre: l'ictère d'origine cérébrale (kernicterus), les complications hémorragiques et l'effet délétère de certaines destructions hépatiques que cette maladie peut occasionner chez l'enfant. La nature des prédispositions constitutionnelles qui font qu'un individu soit plus facile qu'un autre à sensibiliser au facteur Rh n'est pas encore comprise.

Les recherches à venir devraient être concentrées plus particulièrement sur la prophylaxie et le traitement de l'ictère hémolytique congénital. Ce problème ne sera resolu que lorsque des procédés efficaces auront été trouvés pour le traitement des femmes sensibilisées au facteur Rh negatif afin de leur permettre de rendre à terme des enfants normaux à facteur Rh positif.

R. Brault, M.D.

## Sumário

Com os métodos de laboratório de que agora dispomos, é possivel diagnosticar com precisão praticamente todos os casos de doença hemolitica congénita, ou excluir êste diagnostico. É tambem possivel especificar com mais precisão a patogenese, quer devida a isoimunisação para um ou mais dos factores Rh, $Rh_0$, Rh′ e Rh″ ou para os factores Hr ou factores A-B-O.

A maioria das crianças com eritroblastose que nascem com vida podem sêr salvas com transfusões de sangue com o factôr Rh negativo ou com glóbulos vermelhos maternos lavados. Contudo, não se conhece qualquer método eficaz para salvar as crianças dos efeitos mortais de certas injúrias hepáticas mantidas como resultado da doença, assim como de kernicteru ou complicacões hemorrágicas. Não está perfeitamente esclarecida a naturesa da predispasição constitucional que faz com que um indivíduo seja mais facilmente seusibelisado ao factor Rh do que outro.

Trabalhos futuros devem tratar em primeiro lugar, da profilaxia e tratamento da doença hemolitica congénita. Êste problema não será completamente resolvido até que se descubram métodos eficazes para tratamento das mulheres sensibelisadas com o factôr Rh negativo, só assim sendo possivel que elas deem á luz crianças normais com o factôr Rh positivo.

José Ferreira dos Santos, M.D.

## Resúmen

Con los métodos de laboratorio de que disponemos actualmente es posible diagnosticar con exactitud practicamente todos los casos de síndromes hemolíticos congénitos y también excluir este diagnóstico. Es posible también especificar más precisamente la patogénesis, ya sea debida a una iso-inmunización para uno o más de uno de los factores Rh, $Rh_0$, Rh′ o Rh″, ya sea para los factores Hr o para los factores A-B-O.

La gran mayoria de los niños con eritroblastosis que nacen vivos pueden ser salvados por medio de transfusiones de sangre Rh-negativo o de glóbulos rojos de la madre lavados. Sin embargo no se conoce ningún método para tratar efectivamente los niños que sufren de ciertas lesiones hepáticas producidas como resultado de la enfermedad o de ictericias de origen cerebral (kernicterus) o de

complicaciones hemorrágicas. La naturaleza de la predisposición constitucional que hace a un individuo más fácil de sensibilizar al factor Rh que otro no se comprende claramente todavía.

Los trabajos futuros deben encaminarse primariamente hacia la profilaxis y el tratamiento del síndrome hemolítico congénito. Ese problema no podrá resolverse por completo mientras no se descubran métodos efectivos para tratar las mujeres Rh-negativo sensibilizadas, de modo que ellas sean capaces de engendrar niños Rh-positivo.

J. M. Taveras, M.D.

# Post-War Objectives of Tuberculosis Control*

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THE unconditional surrender of Germany and Japan has stopped the shooting. The number of casualties resulting from battle with our enemies will soon be known in quite definite numbers of killed and wounded, but the number of men, women and children who have died, and those who are yet to die as a direct result of the war, will not be fully counted for many years to come.

Our back door enemies—diseases which thrive on war—have not surrendered. Without doubt the most cunning and treacherous of all such diseases is tuberculosis.

It is too early to compute the toll taken by tuberculosis in the countries of our allies and in occupied and enemy territories, up to the end of the war. Dispatches indicate, however, that the disease is rampant in all countries that bore the brunt of hostilities and that tuberculosis was a major cause of death among the starved and tortured internees and prisoners in enemy concentration camps. The presence of tuberculosis remains a most serious obstacle to the recovery and rehabilitation of people freed from prisons, concentration camps and slave labor battalions. Thus the reservoirs of infection in Europe and probably in the Far East have been filled to overflowing and tuberculosis will remain a major problem for a generation at least.

Within the borders of the United States we were mercifully spared the ravages and destruction of total war; but we have lost much ground in the fight against tuberculosis. During the quarter century since the end of World War I, there was a steady and consistent downward trend in the death rate from tuberculosis, but now that decline has almost stopped for the country as a whole, and in some of our States and large cities the death rate has increased by ten percent or more since 1941.

There is some risk of being wrong in predicting future trends but there are definite indications now that conditions brought about by the war will take their toll in the next few years. In the first place, many thousands of men and women moved with their families from farms and small communities to large industrial centers to work in war industries. Some of these people were tuberculous. In this shifting population, those who did not have the disease have been exposed to far greater risk of being infected or reinfected in crowded war plants and congested living quarters than they would have, had they stayed at home. Long working hours, fatigue, faulty nutrition, and dissipation lowered physical resistance in war workers and made fertile soil for the tubercle bacillus. Many people who knew they had tuberculosis were lured by the high wages into war plants against their better judgment. A great many patients left sanatoria against medical advice to do war work, in a short sighted effort to obtain high wages. Many others, found to have tuberculosis in chest X-ray surveys of industrial workers, refused to leave lucrative jobs to enter a sanatorium for treatment. All of these persons have added their quotas of tubercle bacilli to personal environment.

Secondly, our tuberculosis hospitals and sanatoria have been depleted of their medical and nursing staffs because of the necessity for their services in the armed forces. Equally serious has been the loss of laboratory technicians, dietitians and other professional people. Many sanatoria have been compelled to reduce the number of available beds because of the loss of all types of non-professional help to the armed forces or to war plants paying higher wages. Many institutions have been forced to curtail important services to patients and some patients have been deprived of major surgical treatment because of the physical impossibility of rendering the necessary post-operative care.

In the third place, very important field services, including clinic care, have been seriously handicapped all during the war because of the unavailability of properly trained physicians and public health nurses to carry out supervision of patients outside of sanatoria.

* Read at the combined meeting of The Philadelphia County Medical Society and The College of Physicians of Philadelphia, September 19, 1945. Printed in *Philadelphia Medicine*, October 27, 1945.

In addition to these three war-engendered circumstances there remain the same obstacles to adequate control of tuberculosis that have always existed, in peace or war. Some of the more important of these obstacles are concerned with the nature of the disease itself such as the fact that pulmonary tuberculosis may be present but without manifest symptoms until the disease is well advanced; that it is not completely disabling until far advanced; that chronic but infectious disease may exist for years and remain unsuspected especially in elderly people and that there is an innate tendency of the disease to relapse. Another important obstacle to our mastery of the disease is the lack, to date, of a safe chemical or drug to destroy tubercle bacilli in the living human body, making it often necessary to resort to surgery, oftentimes heroic major surgery, to arrest the disease process. Another obstacle is the difficulty of convincing people and, yes, even doctors, that the only sure method of diagnosing pulmonary tuberculosis, or of ruling it out, is an X-ray examination of the chest. There are many more—the difficulty of persuading people to submit to hospitalization and treatment during the minimal stage when the disease is most amenable to bed rest and minor collapse therapy; the difficulty in keeping patients hospitalized until maximum benefit has been derived; and, the difficulty in persuading State legislatures and local appropriating bodies that provision of modern tuberculosis hospitals with an adequate number of beds and with well qualified professional staffs, is an excellent investment.

This brief summary of the problem presented by tuberculosis is enough, I think, to show that here we have a formidable enemy. Yet, this ancient scourge of mankind, in spite of its cunning resistance to the usual protective mechanisms of the body and to therapeutic measures which are effective against other pathogens, is, nevertheless, vulnerable to known methods of attack.

It should always be remembered that once tubercle bacilli become established in the host, it is necessary that tissue be broken down and destroyed in such a manner as to provide an avenue for their escape into secretions and excretions which will carry them outside of the host. This escape is necessary for an opportunity to infect another individual. This fundamental difference between tuberculosis and other respiratory infections is extremely important from the epidemiological standpoint. For instance, in pneumonia the sputum is loaded with pneumococci within a few hours of the onset of the infection and remains so for the duration of the disease. If such a status prevailed in tuberculosis, with all the other characteristics of the disease remaining constant, the problem of controlling its spread would be greatly increased.

In primary infections the tubercle bacilli rarely produce sufficient destruction of tissue to allow the escape of bacilli from the body. People who present evidence of primary infection only by a positive tuberculin reaction or even by X-ray examination can, therefore, be eliminated from consideration as sources of infection. In reinfection tuberculosis there is no such consistency in the type of lesion produced, but, with the possible exception of tuberculous pneumonia, the invading organisms are fixed within the tissues and do not become free in the bronchial secretions until after ulceration into a branch of the bronchial tree takes place. Because of this there is usually an interval of time, often several months, between the creation of a parenchymal lesion demonstrable by X-ray and the finding of tubercle bacilli in the sputum. This is the stage of infection when tuberculosis is most amenable to successful attack.

Full advantage should be taken of this vulnerable minimal stage of the disease. If such lesions could be discovered in large numbers and brought under adequate observation and treatment promptly, the vicious cycle of the disease could be interrupted and the victims prevented from transmitting the disease to others.

This brings us to our first post war objective of tuberculosis control, which is the finding of *every* unknown case of tuberculosis. This is no longer an impossibility. In the few years that radiography, utilizing small films for mass chest X-ray surveys, has been used it has proved eminently satisfactory as a case finding procedure. About 800 persons can be X-rayed in an 8-hour day by one unit, which means that whole populations can be surveyed in a short period of time. Equipment now on the market can produce photofluorographic films of uniform and excellent diagnostic quality. Surveys of over one million people by the U. S. Public Health Service showed that 1.1 per cent had X-ray evidence of pulmonary tuberculosis. Classification of the tuberculous lesions found showed that 65 per cent were minimal; 30 per cent were moderately advanced and 5 per cent were far advanced.

In general population groups where surveys of communities as a whole are as yet impractical,

routine chest X-ray of patients admitted to general hospitals using photofluorographic equipment has been found to be very valuable in case finding. This hospital procedure makes it possible to take necessary precautions so that patients with suspected tuberculosis will not be a menace to the medical and nursing staff and to other patients. In the city of Cleveland, small film equipment for case finding purposes has been recently installed in ten general hospitals. No charge is made to the patient for the routine small film.

Chest X-ray surveys may also be made of industrial employees, office workers, food handlers, inmates and employees of mental hospitals, prisons and reformatories; college and high school students. Whole neighborhoods can be organized for community survey purposes. Studies made in general hospitals in Michigan, Illinois, and New York reveal that as high as 9.3 per cent of patients X-rayed routinely on hospital admission had abnormal chest findings. This is a higher yield of pathology than can be found by the taken-for-granted urinalyses, blood counts, Kahn tests, etc., important as these laboratory procedures are. Physicians could adopt chest X-ray as a routine part of the examination of many office patients to bring about a higher standard of diagnostic accuracy.

The public is being educated to appreciate that a periodic X-ray of the chest on an annual or semi-annual basis is good health insurance. If and when this ultimate objective is reached we will have accomplished our first objective, namely the finding of every unknown case of tuberculosis.

Our second objective is to provide prompt isolation and adequate treatment for tuberculous patients. There are definite things that can be done if we know who has tuberculosis and where it is concentrated, even if there are not enough beds to accomodate all patients. However, States and communities with adequate hospital facilities have a tremendous advantage.

Patients with positive sputum should be isolated from family and other contacts and this can best be accomplished by hospitalization. When this cardinal public health principle has been complied with, the patient is at the same time in the best possible place to receive the close study, observation, supervision, and treatment that modern care of the tuberculous requires if optimum results are to be attained.

Modern tuberculosis hospitals have distinct advantages but until such institutions can be provided we should utilize whatever existing accommodations there may be. For instance, a general hospital can derive distinct benefits by providing proper accommodations for tuberculous patients. This may be a good place to point out that most general hospitals do admit tuberculous patients, policy to the contrary, because the disease is not diagnosed on entry. In 1943, 12,500 deaths from tuberculosis occurred in general hospitals as compared with 20,500 deaths in tuberculosis hospitals and sanatoria in the same year. Not all of these general hospitals, by any means, had regular tuberculosis services. The benefits derived from hospital services in this field are convenient and adequate care for private patients of tuberculosis specialists; development of tuberculosis awareness on the part of the medical staff; a wider range of facilities for diagnostic and consultation services; educational advantages for the staff, medical students and nurses; the teaching of isolation and personnel protection techniques, and good opportunities for the psychological adjustment of the tuberculous patient himself. Hospitals owned by private interests or religious denominations can also benefit by providing beds for the tuberculous. In Duluth, Minnesota, a city of about 100,000 population, special tuberculosis services have been in operation for years in the two main private hospitals (St. Mary's and St. Luke's). Both are approved by the American College of Surgeons, both are approved for interneship training and they both have approved schools of nursing. By special arrangement with the county health department each hospital has set up a special section for tuberculous patients. The county pays a flat annual rate for the beds in these sections whether they are occupied or not. All of the tuberculous patients who are residents of the county are admitted to one of these hospitals rather than being sent direct to the outlying county sanatorium. They receive complete diagnostic services and initial therapy. Later those requiring prolonged care are transferred to the sanatorium as beds become available. If major surgery or special treatment is indicated for sanatorium patients they are transferred back to one of the private hospitals for such service. Tuberculosis specialists are available as members of the medical staffs. These hospitals also maintain tuberculosis clinics for after care and supervision of discharged sanatorium patients.

While diagnostic and treatment clinics for ambulatory patients can not substitute entirely for

lack of hospital beds they are an indispensable part of the tuberculosis control program. The finding of cases is only the first step. Every patient and especially those with minimal lesions requires careful workup. History, physical examination, laboratory tests and additional X-ray films must be taken. Minimal lesions usually require a series of films before a decision can be made as to activity. Patients found to have quiescent lesions require continued periodic observation because of the tendency of the disease to relapse. The importance of keeping minimal lesions under observation has been demonstrated in the British Navy. Brooks,[1] in reporting the results of such observation states that over half a million men and women in the Navy had been examined by miniature radiography: 2911 sailors had minimal lesions and about 1 in 6 of these proved to be active; in 1826 cases the stability of the lesions was uncertain and these were kept under periodic observation. At the time of reporting, some of these cases had been observed for 2 years; 191 or about 9.5 per cent of these suspects developed active tuberculosis while they were being watched; the majority of them relapsing during the first year.

Patients with minimal lesions can often be released from the hospital, after a short period of study, orientation and initial treatment, to continue their treatment as out-patients in private physicians' offices or in well organized clinics. This after care also applies to more advanced cases who have been released from hospitals and sanatoria after long stay. Then there is the usual group of patients who will not submit to hospitalization but who can be induced to remain under observation in a clinic.

More attention should be paid to provision of suitable care for the chronic cases who are not responsive to active treatment. Such patients can be cared for in institutions of a domiciliary or custodial type, thus releasing beds in hospitals devoted primarily to treatment of amenable cases.

Our third objective is the provision of well organized public health administration of the program. There are few States, cities or counties which may be said to have ample tuberculosis control administration. All State health departments and all health departments with jurisdictions of 100,000 or more population need separate divisions or bureaus of tuberculosis control. These should be under the direction of a full time physician who is trained in public health administration and in tuberculosis. This director should be free from political influence and vested with legal authority to receive reports of cases and to enforce compliance with laws governing the control of communicable diseases and tuberculosis in particular. His office should contain a complete register of all known cases. Registers in local health departments should carry all pertinent data regarding cases in its jurisdiction, arranged in such a manner that statistical analysis will reveal the true situation at any given time. The director should have an advisory committee of tuberculosis specialists appointed from the medical society. He should have the complete cooperation of the bureau or division of public health nursing so that prompt and competent public health nursing service may be rendered to tuberculous patients and their families in their homes. The division should have overall control of all case finding activities and supervision of clinics. It should coordinate its activities to render necessary field service required by hospitals and sanatoria. Cooperation and cordial relationship with practicing physicians should be gained and their confidence deserved.

During the war the increased interstate spread of tuberculosis and the need of States and local health departments for financial assistance and personnel to meet the problem led to the establishment of a Division of Tuberculosis Control in the U. S. Public Health Service. In addition to its responsibility for allotments of financial aid to States, the Division furnishes consultation service to State and local health departments; trains physicians, public health nurses and other personnel for loan to States; conducts demonstrations of industrial and other mass X-ray surveys and conducts research in radiology and epidemiology.

The fourth objective is rehabilitation and aftercare for the tuberculous. All 48 States maintain active rehabilitation programs for handicapped people and tuberculous people are eligible for this assistance. Federal assistance to States is provided through the Office of Vocational Rehabilitation of the Federal Security Agency. The community often spends thousands of dollars on the hospital care of a single patient. If after-care and economic rehabilitation are neglected, relapses are likely to occur. Thus the community not only loses the initial investment in hospital care but it is faced with expenditures for additional hospital care and prolonged care of dependents.

[1] Brooks: Lancet, 1944, 1, 745.

To be really effective, rehabilitation and its possibilities should be made known to the patient and to his family as soon as he is faced with necessity for hospitalization. This knowledge can be a powerful factor in prompt acceptance of hospital care. With something tangible to look forward to, the major adjustment both patient and family must make will be undertaken with less misgivings. They will feel that the adjustment is temporary and that in a reasonable time their lives can resume a normal pattern. The United States has lagged behind some of the European countries in the development of rehabilitation. However there have been some demonstrations which have proved their worth and it is expected that these examples will be widely followed.

Our fifth and last objective is protection of the families of tuberculous patients against economic distress. If his family will have to live on a small relief allotment, the tuberculous father with few symptoms will often continue working and delay hospitalization until his disease causes complete and perhaps permanent disability. In the age group 45–64 among white males, tuberculosis mortality is increasing and these are the years of greatest family responsibility. The first four objectives of a tuberculosis control program would operate to hospitalize such patients early, provide rehabilitation, and return the father to self-sufficient status as head of a family. In a family group, however, we are dealing with social and emotional ties, complicated by economic distress. If we can provide dependents with sufficient aid to carry on adequately, in the temporary absence of father or mother, health authorities have a strong argument in favor of early isolation and treatment for the patient and a very effective morale booster for the whole family.

Some aid is available to dependent children of tuberculous parents in 47 states, through the "Aid to Dependent Children" provisions of the Social Security Act. However, the adequacy of the aid thus provided for the family depends upon each individual state, since the Federal contribution is based on the amount provided by the state and county. Each state therefore has within its power the control of what amount will be paid to such dependent children. Social and welfare agencies within the state, by extending this information to the families concerned, can assist the tuberculosis control program immeasurably. This is the only Federal-State cooperative program which can at the present time function to assist the tuberculous family. Probably the answer to the broader problem is National-State legislation providing insurance compensation against loss of wages to tuberculous patients.

Tuberculosis control, as it is defined in terms of objectives, involves more and more professional and technical groups. It draws upon increasing numbers of community facilities and resources. No thinking citizen can escape its implications. To be effective the program must be, and is, progressive and flexible, adapting to its needs all modern knowledge and methods.

Tuberculosis as a disease, we have found, cannot be controlled by a single method or a single group. It is the responsibility of every citizen, every profession, every state and community. If all communities and states concentrate everything they have, and everything they can get, upon the immediate goal of the five objectives, our generation will see the ultimate goal—eradication of the disease.


## Résumé

Cinq problèmes sont discutés: 1) la recherche de tous les cas ignorés de tuberculose; 2) les moyens à prendre pour l'isolement immédiat et pour le traitement adéquat de tous les tuberculeux; 3) l'organisation d'un programme sous l'administration judicieuse du département de la santé publique; 4) le problème de la réhabilitation et de la convalescence des tuberculeux; 5) la protection des familles affligées par la tuberculose contre leurs problèmes financiers.

Le controle de la tuberculose nécessite un nombre croissant de professionnels et de techniciens. Ce controle s'étend de plus en plus aux groupes d'individus qui résident dans une même localité ou qui travaillent en commun. En réalité pour être efficace, ce programme devra être progressif et flexible. On adaptera à ses besoins toutes les connaissances et les méthodes nouvelles. Ceci est la responsabilité de tous les citoyens, de toutes les classes professionnelles et de toutes les communautés.

R. Brault, M.D.

## Sumário

Cinco pontos são discutidos: 1) A descoberta de todos os casos desconhecidos de tuberculose; 2) A possibelidade de rápido isolamento e tratamento adequado para os doentu tuberculosos; 3) A possibelidade de uma administracão de saúde pública bem organisada; 4) Reabilitação e cuidados posteriores dos tuberculosos; 5) Protecção das familias dos tuberculosos contra perturbacões económicas.

O Control da tuberculose envolve cada vez mais a actividade dos grupos professional e técnico. Apela cada vez mais para os recursos e facilidades da communidade. O programa para ser eficaz deve sêr progressivo e clástico, adaptando-se ás suas necessidades todos os conhecimentos e métodos modernos.

É da responsabelidade de todo o cidadão, de toda a profissão e de toda a comunidade.

José Ferreira dos Santos, M.D.

## Resúmen

Cinco objetivos se discuten: 1) el *descubrimiento* de *todos* los casos de tuberculosis; 2) la provisión de *rápido* aislamiento y de tratamiento adecuado para los pacientes tuberculosos; 3) la disposición de una administración bien organizada del programa por la sanidad publica; 4) rehabilitación y cuidado de los tuberculosos después de tratados; 5) protección de la familia de los tuberculosos contra dificultades económicas.

El control de la tuberculosis envuelve cada día un mayor número de técnicos y profesionales. Cada vez atrae un número mayor de recursos y de facilidades otorgadas por la comunidad. Para ser efectivo, el programa debe ser elástico y progresivo, adaptando a sus necesidades todos los métodos y conocimientos modernos. Constituye la responsibilidad de todo ciudadano, de toda profesión, de toda comunidad.

J. M. Taveras, M.D.

# George Eliot's "Quarry for *Middlemarch*": An Unpublished Notebook Revealing Her Medical Sources

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DOCTORS loom large in life and so they loom large in literature. From Chaucer's Doctor of Physic to Dr. Arrowsmith poetry and fiction are full of "counterfeit presentments" of medical men. And the more fiction tended towards the realistic, the more novels which treated problems of medical practice tended to give the reader life-like pictures of doctors. The question of how much Dickens' personal predilections colored his presentation of characters affects our estimate of his medical men. In general, his portraits of doctors seem affected too much by his "reforming" purpose to produce in the reader any sense of reality. Dr. Bayham Badger in *Bleak House* is too bad, Allan Woodcourt is too good. His medical students may reflect the chaotic conditions in the private institutions for medical teaching, but their coarseness and irresponsibility strike most readers as the product of Dickens' caricaturing pen. Thackeray's pen had a slant, too, but his Dr. Goodenough in *Pendennis* has much more reality than the wooden Allan Woodcourt, though he, too, suggests an overdose of idealism in the basic conception of his character. It may be interesting to note that Dr. Goodenough was the portrait (as much as any figure in a truly imaginative literary work can be said to be a portrait) of Dr. John Elliotson, the doctor who had seen Thackeray through a severe attack of illness and to whom he dedicated this very book. Dr. Elliotson was a leader in the medical profession whose later adherence to phrenology and mesmerism wrecked a distinguished and useful career. A tragic story could be written of his life.

Many Victorian novelists give us representations of doctors, but the medical figure who has received the most praise from doctors themselves is Lydgate in *Middlemarch* by George Eliot, who, Sir S. Squire Sprigge says, "spoke nobly on the side of the medical profession."[1] Dr. Garrison, in his voluminous history of medicine, says, "The best imaginative portrait of the intellectual type of physician is that of Lydgate, in George Eliot's *Middlemarch*, a novel which, on the whole, affords the most effective side-light on English medicine in the late Georgian and early Victorian periods."[2] Dr. Gerald B. Webb[3] and Dr. H. A. Derow[4] have also praised the fidelity of Lydgate's character as an ambitious young physician of his time. But the tribute most prized by *Middlemarch* admirers is that of a master of medicine who was also a scholar and a critic of literature, Sir William Osler. In Dr. Cushing's *Life of Sir William Osler*,[5] we find the following invaluable information and criticism, which is worth quoting at length:

"Ask the opinion of a dozen medical men upon the novel in which the doctor is best described, and the majority will say *Middlemarch*. Lydgate is at once an example and a warning . . . An unmitigated calamity, his marriage ruined his intellectual life in a soul-wasting struggle with worldly annoyances . . . George Eliot was happy in her relations with the profession, and we owe her a deep debt for this Early Victorian sketch of it in a provincial town. It is often said that my Brother Regius of Cambridge, Sir Clifford Allbutt, was the original Lydgate. Nothing in their careers is in common, save the training and the high aspirations. There is a basis for the statement. When Dr. Bastian lived at Hanwell, one Sunday afternoon he had just returned from a visit to George Eliot, and the conversation turned on *Middlemarch* which had recently appeared. He said that the matter had been discussed in her house that afternoon, and she confessed that Dr. Allbutt's early career at Leeds had given her suggestions."

[1] *Physic and Fiction*, London, 1921, p. 60.

[2] F. H. Garrison, *An Introduction to the History of Medicine*, Phila., 1929, p. 754.

[3] *Medical Life*, **36:** 192–218, 1929.

[4] *Annals of Medical History*, **9:** 358–363, 1927.

[5] Oxford, 1925, vol. 1, p. 463 (footnote).

What gives the book this prestige among doctors who are also interested in literature? The answer, of course, demands a study of the question, "Does *Middlemarch* really reflect the conditions in the medical world of provincial England in the year 1830?" A true and convincing answer would entail an exhaustive knowledge of the history not only of medicine but of the *practice* of medicine in early nineteenth century England. This equipment I do not possess, but I can offer a little pertinent information on the subject gleaned from a small Ms. note-book now in the Houghton Library at Harvard University.

In 1923, the late Amy Lowell purchased from the Lewes family, through Sotheby, a small, black leather note-book, whose paper label was endorsed in the handwriting of George Eliot, "Quarry for *Middlemarch*". At Miss Lowell's death her library passed to Harvard and this little working note-book was kept in the room devoted chiefly to poetry along with Miss Lowell's collection of Keats Mss. The study of this book gives us a unique opportunity to see how a great novelist gathered information and ideas which made the times and the people of her book convincing.

Having filled the first half of her note-book with quotations and notes which gave her an understanding of the problems that would have confronted an eager minded young doctor in England in the years from 1829 to 1832, she turned the book over and used the pages of the second part to note down some of the social and economic information she needed and to plan out the eight books of the novel with their total of eighty-five chapters. This part of the book is fascinating study in the actual composition of a work of fiction, but it is the first part which gives *Middlemarch* the values that Osler and other medical appreciators have found in it. To this part of the note-book, then, let us turn our attention.

The notes in the first part of the *Quarry* may be summarized as follows:

*Pp. 1–8:* Quotations from the London *Lancet*, mostly from the years 1830 and 1832.

*Pp. 9–10:* List of books by or statements of accomplishments of Schleiden, Schwann, Malpighi, Swammerdamm, Lyonnet, Hewson and Ehrenberg.

*Pp. 10–16:* Notes from a book entitled "An Exposition of the State of the Medical Profession in the British Dominions & of the injurious effects of the monopoly of usurpation of the Royal College of Physicians in London", published in 1826. Some of the points covered in the notes from this book are:

Restrictions on the practice of medicine from 1519 on;

The constitution of the Royal College of Physicians, i.e., the elements that composed it and how vacancies were filled;

The gradual elevation of graduates in medicine of Oxford and Cambridge to dominating positions;

The inferiority of the education given in these institutions to that given in Edinburgh;

The same restrictive narrowness characteristic of the College of Surgeons as appeared in the College of Physicians;

The inefficient, even stultifying, action of both colleges in such great medical inquiries as those on Contagion and Lunacy.

*Pp. 16–19:* A summary of the history of the differentiation of typhus and typhoid fevers, from the work of Prost in 1804 to that of Gerhard and Pennock of Philadelphia in 1836, with special mention of the "celebrated treatise" of Louis in 1829;

Notes taken from Sir Thomas Watson's *Lectures on the Principles and Practice of Physic*, section on "Fever", pp. 825–862. The notes deal, for the most part, with treatment. The edition I used to check these notes was published in Philadelphia in 1844; probably George Eliot used one of the later English editions.

*P. 20:* A quotation from T. H. Huxley's essay-review in the *British and Foreign Medical and Chirurgical Review*, vol. XII, 285–314. This note deals with the work of Bichat.

*Pp. 21–22:* A passage from F. V. Raspail's *Nouveau système de chimie organique fondé sur des nouvelles methodes d'observation*, etc., Bruxelles, 1839, vol. I., 362. George Eliot's note was taken from the edition of 1833. The quotation suggests the existence of a fundamental animal tissue "which plays in animals the same role as that played in vegetable life by cellular and vascular tissues."

*Pp. 23–28:* These pages are filled with: (1) suggestions of possible mottoes for the chapters of the novel; (2) facts taken from the *Annual Register* of 1830; (3) an unidentified statement about "Peruvian bark" and the explanation of its apparent failure to cure "the ague"; (4) miscellaneous notes on (a) the injustice of the poor-rate and of tithes and (b) the uses of manganese.

*Pp. 28–29:* A note from the *Annual Register* of 1832 which deals with the history of the cholera

epidemic of 1831–32 in England. George Eliot's satiric attitude towards Parliament's view of the cause of cholera is shown by her quotation of the following statement, "In the bill for Scotland the House actually divided on the question whether words which spoke of the disease being an infliction of 'providence' should be part of the preamble. Six members, headed by Mr. Hume, voted for their exclusion. They had been omitted in the preamble of the English bill, but were inserted in the House of Lords."

*Pp. 29–31:* Notes from *Remarks on the History & Treatment of Delirium Tremens*, by John Ware, M.D., published in Boston in 1831. Dr. Ware advocated the so-called "expectant method", the withdrawal of stimulants and the treatment of sleeplessness as a natural accompaniment of delirium, not as an indication for large doses of opium. This method of treatment was in contrast to that advocated by most British doctors at that time.[6]

How do the information and the ideas which George Eliot gleaned from this reading and set down in these notes appear in the text of *Middlemarch*? It is not possible in a brief space to show in detail how each note was used, but we can run over the various important entries and get a general idea of the way in which they contribute to the impression of reality that the novel still gives us today.

In general, we may say that the *Lancet* notes were used chiefly to give readers a sense of the actual problems that confronted medical men in 1830–32, especially medical men in a small, provincial city. Of prime importance, perhaps, was the question of medical reform. Lydgate is pictured as an eager, forward-looking young man, anxious for his profession to throw off the shackles of outworn theory and of hampering modes of practice. The medical world was awake; in Paris reform was in the air, in England, too, things were moving. For example, the very first *Lancet* note refers to the abortive attempt in 1830 to elect a medical man for coroner in the county of Middlesex, and many pages of the notebook are devoted to criticisms of the cramping effect of the two great colleges.

Fees, too, came in for their share of attention, especially the new and horrifying change that made it legal for a general practitioner to charge for his services as well as for the drugs with which he treated his cases. The problem of fees was a double-edged one. They must be small enough so that poor persons could have good medical attendance and they must be large enough so that the medical man himself need not be penalized for his interest in caring for poor people. Scales of fees were proposed in many letters to the *Lancet*, one of which (although this is not noted in the *Quarry*) gave at length the scale of fees in use in New York at about that time.

Another subject discussed in the *Lancet* notes is medical education. The weakness of the training offered in London was contrasted with the more thorough work done in the Edinburgh schools. The scarcity in London of bodies for dissection and the refusal of the London authorities to count dissection done outside the confines of their jurisdiction in considering a candidate's fitness to practice were pointed out as a cause of backwardness in surgery.

The cholera epidemic occupied many pages of the *Lancet* itself during 1831 and 1832, but received only one short entry in the *Lancet* notes, though a longer note taken from the *Annual Register* shows that the accounts of the catastrophe made a great impression on George Eliot's mind.

All these topics are skilfully woven into the texture of *Middlemarch*, cropping up in a very casual manner in the conversations between the medical men or in talk about them by the people of the town. For example, the decision that practitioners had a right to charge for services as well as for drugs crystallizes in the following passage in chapter 45:

"One of the facts quickly rumored was that Lydgate did not dispense drugs. This was offensive both to the physicians whose exclusive distinction seemed infringed on, and to the surgeon-apothecaries with whom he ranged himself; and only a little while before, they might have counted on having the law on their side against a man who without calling himself a London-made M.D. dared to ask for pay except as a charge on drugs."

Passing to the *Quarry* notes which are taken from other sources than the *Lancet*, we find some of them reinforcing information on general topics of medical interest already introduced in the *Lancet* material. One such case is the matter of the attitude towards the Colleges' cramping effect on medical education and medical practice, which appears in the six pages of notes drawn from the *Exposition*.

[6] Dr. Garrison (*op. cit.*, p. 754) says of this work that it "is, in connection with the earlier paper of Thomas Sutton (1813), the classic account of this neurosis."

But the great majority of these non-*Lancet* notes have to do rather with the building up of Lydgate's character, with his interest in research and with his actual practice of medicine. For Lydgate was "fired with the possibility that he might work out the proof of an anatomical conception and make a link in the chain of discovery" (Chapter 15). The notes on Schleiden, Schwann, Malpighi, etc. are not directly used in the text of the novel, but the notes from Huxley's review and from Raspail's book form the back-ground of the dreams and hopes of the young doctor who wished not only to be a good practitioner of medicine but to carry forward some phase of scientific discovery. The work of Bichat fascinated him with its illumination of the problems of structure. Part of Chapter 15 in *Middlemarch* deals especially with this aspect of Lydgate's ambition. He was "enamored" of the possible sequence to Bichat's work; "he longed to demonstrate the more intimate relations of living structure, and help to define men's thoughts more accurately after the true order." "What was the primitive tissue? In that way Lydgate put the question..." And he planned to use "not only the scalpel", but "the microscope, which research had begun to use again with new enthusiasm of reliance". In Chapter 45 he says, "I am more and more convinced that it will be possible to demonstrate the homogeneous origin of all the tissues. Raspail and others are on the same track..." He is interested also in discoveries more directly connected with the practice of his profession. In Chapter 16 he feels sure that he will not marry for five years at least and turns "to look into Louis' new book on Fever, which he was specially interested in because he had known Louis in Paris, and had followed many anatomical demonstrations in order to ascertain the specific differences of typhus and typhoid." His interest is a scientific one chiefly at that point, but later we see him putting his knowledge to good use in his practice.

For Lydgate has a very real sense of devotion to his work as a practitioner. "I should never", he says, "have been happy in any profession that did not call forth the highest intellectual strain, and yet keep me in good warm contact with my neighbors. There is nothing like the medical profession for that..." And to give us a sense of this side of Lydgate's work George Eliot presents us with a number of his "cases". The first time we see him actually caring for a patient is when he is called to see Fred Vincy, the young man whose father is mayor of Middlemarch and whose sister Rosamond is to be Lydgate's undoing. Here his reading of "Louis' new book" stands him in good stead and under his care young Fred recovers. The *Quarry* notes which gave the background for this incident shows theat George Eliot was interested in the clash of opinion, about 1830, as to the real nature of "continued fevers", between the majority of English doctors and the ones who were keeping up with continental research.

One of the most important cases that Lydgate was called in to see was that of the clergyman, Mr. Casaubon, husband of the woman who, we cannot help feeling, should have been Lydgate's wife. Casaubon has an attack of "heart disease", and Lydgate finally tells him (Chapter 42): "I believe that you are suffering from what is called fatty degeneration of the heart, a disease which was first divined and explored by Laennec, the man who gave us the stethoscope, not so very many years ago." There are no notes in the *Quarry* which seem to have any bearing on this case, but on page two of the note-book, we find a mention of a review in the *Lancet* of "Elliotson on diseases of the Heart", with a suggestion of one aspect of the review, "Laennec's discoveries as to the symptoms." If we look carefully through this book of Elliotson, we can hardly escape the suspicion that George Eliot, too, read it, though it is hard to say exactly what she got from it. George Henry Lewes, who had a great deal to do as encourager and critic with every novel she wrote, knew many doctors and had a fair knowledge of some aspects of medicine, and we have to take into account always the information the novelist may have got from him. The reading which is reflected in the *Quarry* notes was not by any means her only important source of ideas and material used in the medical part of *Middlemarch*. One of Lydgate's cases does not seem to have found any support from the reading recorded in the note-book. This is the case of "the eloquent auctioneer", Mr. Borthrop Trumbull, who was suffering from pneumonia. Again we find Chapter 45 useful; Lydgate tries "the expectant theory" on Mr. Trumbull, "who was a robust man" and so "a good subject for trying a new treatment upon, watching the course of an interesting disease when left as much as possible to itself, so that the stages might be noted for future guidance." The patient "went without shrinking through his abstinence from drugs, much sustained by application of the thermometer..., by the sense that he furnished

objects for the microscope, and by learning many new words which seemed suited to the dignity of his secretions."

The case of Mr. Trumbull is not of any great importance in the "plot" of *Middlemarch*; it merely helps to show Lydgate's up-to-dateness and the fact that his practice was growing. But the last of the *Quarry* notes in Part I furnishes us with the background for what is a determining incident in the catastrophe which overtakes Lydgate. This is the *delirium tremens* case of the man who might be called the assistant-villain in the piece. Dr. Ware's book seems to have suggested the treatment used on "Mr. Raffles" and a nice point underlies the author's choice of this particular method of doing away with him. The majority of the English doctors of the day seem to have favored more drastic treatment than Lydgate, following Ware, used; so, even though he suspects that Bulstrode, who has the strongest of reasons to wish Raffles out of life, has interfered with his treatment, Lydgate knows that any attempt to bring Bulstrode to judgment would not succeed because his interference with the "Ware method" would have appeared merely good sense to any ordinary group of English doctors who might be called on to give testimony. I could find no review of the American Dr. Ware's book in the *Lancet* (though that does not prove there is not one lurking in an obscure corner) and it would be interesting to know where George Eliot got on the track of the book which proved so useful to her in giving some semblance of reality to the most melodramatic episode of her novel.[7]

The fact that *Middlemarch* seems, as Dr. Garrison asserted, to cast a "most effective sidelight on English medicine" of the times, and that its hero's ambitions and experiences appear "real" to us and not just "made-up" is partly the result of what the *Quarry for Middlemarch* represents, an earnest effort to know the medical problems of that time. But all that effort would have been a detriment rather than a help if George Eliot had not been something besides an indefatigable collector of facts, more than a most intelligent student of medical history—if she had not been, in short, an artist.

[7] In view of the general ignoring by British doctors of American medical work in the 1830's it is all the more interesting that George Eliot should have found this publication by Dr. Ware and in it a clever way to make Lydgate's dilemma a logical one. I hope some time to find a reference to the Ware book in some medical review of the period with which *Middlemarch* deals.

# Benjamin Rush Terminates a Post-War Mutiny among Troops Demanding Their Discharge

*By* JAMES E. GIBSON
*Philadelphia, Pa.*

THIS is a hitherto untold account of Doctor Benjamin Rush's claim that it was through his effort that the mutinous Continental soldiers, who picketed the Pennsylvania State House in 1783, capitulated to the authorities and returned to their camp.

The Revolutionary War fighting was finished, but a large number of soldiers were still held in service, pending drafting of the formal Peace Treaty in Paris and the withdrawal of British troops from America. During that inactive period of waiting, military discipline became lax and the men more conscious of their own needs and sufferings. Muttered complaints developed into loud angry protests and finally found expression at Newburgh, New York, in anonymously printed pamphlets circulated throughout the Post, calling upon the troops to resort to open revolt if redress of their grievances was not immediately obtained.

General Washington was greatly disturbed by this threat of mutiny, and in an Order of the Day, summoned the "General and Field Officers, with one from each Company, and a proper representative from the Staff of the Army, to assemble and hear a report of a Committee of the Army to Congress". At this same time, he intimated his expectation that the assembled officers would repudiate authorship of the pamphlets and declare their loyalty to all persons in authority. Many of those present were in complete sympathy with the plans suggested in the objectionable documents, but out of affection and regard for their Commander-in-Chief, they unanimously adopted a Resolution, saying: "The Officers of the American Army view with abhorrence, regret and disdain the infamous propositions contained in the late anonymous address, circulated in the Camp."

General Washington made a full report of the incident to the President of Congress, and the pamphlets, with the Resolution passed by the officers, are recorded in the Journal of the House.

An account of the disorder at Newburgh was given great publicity in the newspapers of the Colonies and served to encourage the soldiers in other camps to voice their own discontent and dissatisfaction with conditions. Food was scarce; clothes were in rags and pay long overdue. They contended the war was over and they could not understand why they should not be paid off and permitted to go home.

Congress attempted to satisfy some of the soldiers' complaints by a Resolution dated May 26, 1783, offering payments in cash for the previous January's service, with six-month notes for amounts due each man for February, March, April and May. The legislation also provided that the veterans might have a choice of leaving on furlough at half pay or of remaining in camp with full compensation until discharges from the Army were authorized.

This expediency was a necessary one, for sufficient currency was not available to settle all existing claims, and Robert Morris' efforts to negotiate credits abroad were meeting with difficulties.

The solution of this situation, enacted by Congress, was not made known to the Army until several weeks had passed, and it was on June 16th that the troops encamped at Lancaster, Pennsylvania, were informed through the published orders of the day. The reaction of these soldiers was immediate and positive, as reported by Colonel Richard Butler, Commander of the Post, in a hastily written letter, dated 10 A.M., June 17th, to John Dickinson, President of the Pennsylvania Supreme Executive Council at Philadelphia.

"Early this morning a committee of Sergeants called at my quarters and informed me the men were determined to go to Philadelphia in order to obtain justice. I made use of every possible argument to show them the impropriety of such action, and they went away contented, as I thought, but soon afterwards I was informed the soldiers were getting ready to leave in a body. I immediately went to the Parade Ground, accompanied by a number of my officers including Colonel Samuel Atlee, who happened to be in town. We formed in a circle and I talked to the

men as before, but to no purpose, and a large number left camp at half past eight o'clock A.M. I gave the soldiers every assurance of an immediate cash payment and of their all being kept here together until a settlement is completed.

"I have conferred with the officers of the Post and we are of the opinion that one of us should follow the mutineers and make another effort to bring them back. If this fails, I give it as my belief that no settlement should be made with them until they return to the camp; otherwise, it will be too great a condescension and give encouragement to others at some future day, as well as being humiliating for officers to be obliged to follow mutineers and attempt a settlement on a basis that had already been offered and insolently refused (1)."

Later in the same day a second notice of the movement of these Lancaster men was sent to John Dickinson by William Henry,[1] reading:

"Eighty armed soldiers set off this morning for Philadelphia to cooperate with those now in your City in such measures as may appear to them to most likely procure their pay.

"I have thought it my duty to give you this timely information in order that the City may not be surprised. I am also informed that part of General Armand's Corps will arrive here tomorrow, and from what has transpired here and from what I learn, I believe General Armand's men will follow the others to your City and share in the same fate. The soldiers have thrown out threats that they intend robbing the Bank and the Treasury." (1)

The Journal of the Continental Congress, dated June 19, 1783, records:

"Information is received from the Executive Council of Pennsylvania that eighty soldiers, who may be followed by the discharged men of Armand's Legion, are on their way from Lancaster, declaring they will proceed to the seat of Congress and demand justice, and with the intention of a design against the (U. S.) Bank." (2)

Whereupon, the following order was sent to Major Jackson, Assistant Secretary of War:

"Sir: Information having been received that a detachment of mutineers are on their way from Lancaster to this place, you will proceed to meet them en route and endeavor by every prudent means to persuade them to return to the Post they have left. You will inform them of the order that has been given, permitting them to remain in service until their accounts have been settled or, if they prefer, of being furloughed with an allowance of the pay which has been granted the Army at large. You will represent to them that their accounts cannot be settled without the aid of their officers whom they have left behind at Lancaster. You will represent to them with coolness but with energy, the impropriety of their irregular proceedings and the danger they run by persisting in such improper conduct. You will assure them of the best intention in Congress, to do them justice and of the absurdity of expecting to procure it more effectually by intemperate proceedings.

"You will point out to them that such proceedings as they have taken, may arouse the resentment of the entire country and indispose it to approve effectual measures for their relief. In short, you will urge every consideration in your power to induce them to return to Lancaster, but at the same time avoiding whatever may tend to irritate. If they persist in coming to Philadelphia, you will send us the earliest possible notice. Should they want provisions, you may assure them of a supply and you will endeavor to procure same, in preference to their coming to Philadelphia." (2)

The following day, June 20th, the Journal recorded: "The soldiers from Lancaster have arrived in the City under guidance of their Sergeants. They profess to have no other object than to obtain a settlement of their accounts for which they suppose they have a better chance in Philadelphia than at Lancaster." (2)

There were, at that time, several hundred soldiers stationed in Philadelphia who had already petitioned the Pennsylvania Supreme Council for consideration of their complaints, with a request for cooperation in obtaining redress from Congress. Their efforts had been without threats, but when the mutineers arrived and quartered themselves in the same barracks, many of the Philadelphia troops indicated a willingness to join in more violent methods to obtain action (2).

On Saturday, June 21st, three hundred soldiers, with fixed bayonets and drums beating, marched to the State House. They surrounded the building, placed guards at every door and sent in a delegation with the following note:

"We, the non-commissioned officers and soldiers in this City, demand of you the Honorable Council, authority to appoint commissioned officers to command us and to seek redress of our grievances,

[1] Gunsmith and patriot, of Lancaster, Pa., member of the Continental Congress, 1784–6.

such officers to have full power to adopt measures they may judge most likely to procure justice. *You will immediately issue such authority and deliver it to us, or otherwise we shall instantly let loose upon you, those injured soldiers, and abide by the results. You have only twenty minutes to deliberate on this important matter.* Our (old) officers in general have forsaken us and refuse to assume any further command. This we presume you all know." (1)

The Minutes of the Continental Congress record the incident as follows:

"The mutinous soldiers presented themselves, drawn up in the street before the State House where Congress was assembled. The Executive Council of Pennsylvania setting under the same roof, was called on for a proper interposition. President Dickinson appeared before us and explained the difficulties of calling out the State Militia for the suppression of the mutineers. In the meantime the soldiers remained in their position but without any violence though some individuals occasionally uttered offensive words and wantonly pointed their muskets at the windows of the Hall of Congress. No danger from premeditated violence was apprehended, but it was observed that spiritous drinks from nearby tippling houses were liberally served the soldiers, and it was feared might lead to hasty excesses. None were committed however, and about three o'clock, the usual hour, Congress adjourned, and the soldiers, though in some instances offered mock obstructions, permitted our members to pass through their ranks." (2)

While the mutineers were picketing the State House, Congress dispensed with the intended agenda for the day and devoted itself to the problems of the existing crisis, resolving:

"That the President of the Supreme Council of Pennsylvania, be informed that the authority of the United States having this day been grossly insulted by the disorderly and menacing appearance of a body of armed soldiers surrounding the place within which Congress is assembled, and the peace of the City being endangered by the mutinous disposition of said troops now in the Philadelphia Barracks, it is the opinion of Congress there is a necessity that effectual measures be immediately taken for supporting public authority, and it is further resolved that a Committee be appointed and directed to confer with the Supreme Executive Council of Pennsylvania, on the practicability of carrying the preceding resolution into effect: In case there is no satisfactory ground for expecting adequate and prompt exertions by the State authorities for supporting the dignity of the Federal Government, the President of Congress, on advice of the Committee, is authorized and directed to summon the members of Congress to meet on next Thursday (June 26th) at Trenton or Princeton in New Jersey, in order that further and more effectual measures may be taken for suppressing the present revolt and maintaining the dignity and authority of the United States." (2)

Another Resolution was passed directing the Secretary of War to inform the Commander-in-Chief of the situation, in order that he might dispatch such troops as he might deem necessary to suppress any disturbance that might ensue (2).

During the next day, a Sunday, the soldiers remained in Barracks, but reports that filtered out gave no comfort to the authorities. At first, however, it was reported the men were penitent, but a little later it was said they planned taking even more violent measures. Some favored an attack upon the Bank, while others suggested that certain members of Congress be seized and held captive until the desired legislation were passed, and a full pardon granted to all those who took part in the mutiny (1).

The Pennsylvania Supreme Council declined to call for aid from the local militia, claiming lack of authority unless some overt act were committed or property destroyed, so on Tuesday, June 24th, all efforts to disperse the mutineers having failed, the Committee of Congress advised its President to adjourn the Body and reassemble at Princeton (1).

Among the manuscript collections in the Ridgeway Library is a copy of a letter written in 1812 by Doctor Benjamin Rush (3). The name of the person to whom the original was sent is not included, but internal evidence proves it to have been John Adams, with whom the doctor exchanged many reminiscing letters. It began: "My dear old friend:

"In giving you the history in my last letter, of the controversies in which I was engaged with the Military Hospitals, and from which I suffered much abuse and received the lasting resentment of the *Character*,[2] I neglected to mention in addi-

[2] There was no assurance of privacy in the mail during the early days of the Republic. Many men used codes for protection, and Adams and Rush, fictitious names when referring to persons of prominence. "The Character" was the one chosen for Gen. Washington.

tion to the charges which my resignation produced that my zeal and suffering on behalf of the sick soldiers produced another event, the history of which is not known.

"Walking one afternoon near the Barracks where the mutinous Pennsylvania soldiers had taken refuge in our City, I met two or three of the leaders of that body. Entering into conversation, I urged them to lay down their arms and make peace with the authorities. They listened with attention to my advice and after a while, one of them asked whether I thought the Government would accept their submission without punishing them. I replied that I believed that this could be arranged, but I would in a short time satisfy them on that point. I immediately went to Mr. Dickinson who was then the President of the Executive Council of our State, and informed him of what had passed between me and the leaders of the mutiny. Dickinson seized on the idea of promising them a pardon with avidity, and requested me to return with his assurance that if they would lay down their arms and return to Lancaster, as soon as possible, he would be their intercessor with the General Government, and that he had no doubt of success. I returned with quick steps to the Barracks and delivered Mr. Dickinson's message. The leaders of the mutiny immediately convened all of the Pennsylvania Line men and addressed them in a manner suited to the subject. Some of them asked what security was there that Mr. Dickinson did not mean to entrap them, and one of the leaders replied; 'Here is our security'; this is Doctor Rush, I know him well, (alluding to my sympathy with their suffering and their grievances) 'He will go with us to President Dickinson's. Yes, I will; said I. They then placed me with their leaders in the front rank and followed us to the home of Mr. Dickinson. He came out of the house, accompanied by a servant holding a candle, and addressed the soldiers in a pathetic and sensible speech, repeating the assurance to them that he had given me, of his determination, if possible, to procure their pardon. They gave him three cheers, marched away from his door, and with a Field Officer in command, they left for Lancaster. Say, my friend, was not that a triumph over prejudice and an ample reward for all I had suffered for my attachment to the cause of Justice and Humanity?"

The incident recorded in Rush's letter evidently occurred on June 26th, two days after Congress abandoned Philadelphia, for under that date John Dickinson hastily dispatched a messenger to the President of Congress, saying "Colonel Hampton this moment informs me that the soldiers from Lancaster have laid down their arms and submitted. Their Sergeants have fled (1)."

The following day Dickinson amplified his previous note with:

"Yesterday evening the soldiers from Lancaster began their march toward that place, under command of officers. Those remaining in the Barracks are behaving very quietly, but are desirous of receiving a discharge from the Army. Colonel Hampton informs me that letters were sent by the leaders of the late disturbance to General Armand's Legion of Colonial Troops, inviting them to join in the mutiny. The present disposition of Armand's force I know not, but I expect to receive prompt advice of any movement of importance among them, which I shall immediately communicate to Congress (1)."

Conscious that their participation in the demonstration before the State House had laid themselves open to serious charges, the Philadelphia Barracks soldiers appointed a committee of non-commissioned officers to make their peace with the Supreme Executive Council. The first attempt was by a communication in which they declared they had only joined in the mutiny staged by the Lancaster soldiers, because they feared for their lives if they refused; and they further claimed that by so doing, they had prevented even greater mischief. The Council declined to consider their appeal for a pardon until a complete submission was addressed to the Continental Congress (1). This condition being met, the soldiers submitted a petition to the Council which in part, was as follows:

"May it please your Excellencies for us to submit our reasonable requests for your consideration.

"First. We request one half of the pay that may be due us on the date of our discharge. The four months settlement offered, we think unfair, as some soldiers have not served more than a total of five months, while many of us have three years pay due.

"Second. The balance that may be due after receiving cash as above, we desire to be settled with Certificates (of indebtedness) bearing lawful interest and a definite date of redemption, so that they may be useful in case of sickness or other unavoidable misfortune.

"Third. We expect our small allowance in rations, promised us at the beginning of the war,

but cut off since, shall be made up, and that all deficiencies in clothing shall be settled for.

"Fourth. That we shall receive Patents for land promised us with our discharge, including His Excellency's gratuity.

"Fifth. That all soldiers already discharged from Headquarters may be included agreeable to their merits; also all those yet to be discharged, and particularly those who have lost a limb.

"Sixth. That the settlement here requested may extend to all soldiers belonging to the Pennsylvania Line wherever they may be in these United States.

"Seventh. That the troops which came from Lancaster may be put on equal footing with us as soon as possible.

"These are all the requests your hardy veterans have to make. We think them our right and we hope to obtain them. Should the Public good ever again need our services, we declare (a willingness) to sacrifice our most endearing connections to again serve (1)."

To what extent this petition was granted is not a matter of record.

Complete submission having been obtained, John Dickinson informed the soldiers of the Philadelphia Barracks that in consequence of their penitence and promise of future good behavior, he would recommend that Congress grant a full Federal pardon (1).

One of the first resolutions adopted by Congress at Princeton was an order to General Howe of the Continental Army, to apprehend all persons belonging to the Army who were believed to have instigated the late mutiny and to bring them to trial (2).

On August 13th, the President of the Court Martial reported to Congress that two of the officers tried, had been acquitted; two had escaped, and that two Sergeants were condemned to die, while four soldiers were to receive corporal punishment. Congress directed that the execution of these sentences be deferred until they could further consider the matter (2).

One month later, on September 13th, a Congressional Resolution was passed, reading:

"WHEREAS, at a General Court Martial held near Philadelphia for trial of persons promoting or concerned in the late mutiny of part of the Pennsylvania Line Regiment stationed at Lancaster, Pennsylvania, and in the Barracks of the City of Philadelphia, Christian Nagle and John Morrison, late Sergeants of the 3rd Pa. Regi. were charged with, and convicted of, a breach of the Third Article of the second section of the Rules and Articles of War, and by an action of the said Court were sentenced to suffer death; and whereas also were Gunner Tilly and drummer Horn of the 4th Pa. Artillery, and Thomas Flowers, and William Carman, soldiers in the 3d Pa. Regi. were charged and convicted of a breach of said Articles of War and sentenced to receive Corporal punishment; and whereas, the said mentioned persons do not appear to have been principals in said mutiny, and as no lives were lost, nor any property destroyed, NOW KNOW YE, that by our special grace and the virtue of the power and authority vested in us by the Articles of Confederation, the United States Congress assembled have thought fit to grant a full, free and absolute pardon and remission to Christian Nagle, John Morrison, Gunner Tilly, drummer Horn, Thomas Flowers and William Carman, and to each of them, of all judgements or sentence of death or other corporal punishment, pain or penalty whatever given or awarded by the General Court Martial (2)."

1. John Dickinson papers, Library of Congress, Washington, D. C.
2. Journal and Records of the Continental Congress.
3. Rush Mss., vol. 29, p. 120[4]. Ridgeway Library, Philadelphia, Pa.

# Memoir of James Addison Babbitt*

*By* GEORGE M. COATES

IN the death, on October 15th, 1944, of Dr. James A. Babbitt, the College of Physicians of Philadelphia lost one of its most distinguished Fellows, the medical profession of Philadelphia and the nation a very noted Otolaryngologist, and a host of men and women, lay and professional, a most loyal and untiring friend. His death, although not unexpected, was nevertheless a shock to most of us, although the long period of illness, dating from May of 1944 and starting with a hemiplegia, had prepared us for the worst. Having apparently made a good recovery and most of the traces of paralysis having disappeared, he resumed his work and most of his many other activities in September, only to rapidly succumb to a return of his previous pathology.

Jim Babbitt was born in Waitsfield, Vermont, on October 22nd, 1869, the son of the Rev. James Howard Babbitt, a Congregational Minister, and of Mary French Abbott, both New Englanders of old colonial stock. His boyhood years were all spent in New England, where his father held charges in Waitsfield, Swanton and West Brattleboro, all in Vermont, and where he attended school until 1885. He attended Phillips Academy, Andover, until 1889 and from there he entered Yale University, graduating with an A.B. in 1893, and while in this latter institution he was a member of the football squad and developed the keen interest in all forms of physical training and competitive athletics that he maintained throughout the years. Intending to eventually study medicine, he obtained the position of physical director and teacher of anatomy, bacteriology and physiology in Haverford College, eventually becoming Professor of Hygiene and Physical Education, which position he held until his retirement as Emeritus Professor not so many years ago. Although brought up as a Congregationalist, his many years of close association with students, faculty and trustees of Haverford College engendered in him a love and admiration for the customs and theology of the Society of Friends and he became an associate member of the Haverford Meeting. He had a sincere spiritual nature and practiced his beliefs. At an early wartime meeting of the Council of the American Laryngological Association, the then President, entirely unexpectedly, asked Dr. Babbitt to open the meeting with a prayer. This had never been done before but without hesitation or preparation he delivered one of the most beautiful and heartfelt prayers that it has ever been my good fortune to hear.

After two years at Haverford, Dr. Babbitt was married, in 1895, to Mary A. Adams, of Swanton, Vermont, and the same year began his medical studies at the University of Pennsylvania, at the same time continuing his College work and teaching. He graduated from this institution in 1898, but in the meantime, in 1896, was awarded the degree of M.A. by Haverford and later on the honorary Phi Beta Kappa. Even a superficial consideration of these overlapping dates will show the enormous capacity for work, both physical and mental, that he was capable of, and which was to set the pattern of his entire subsequent life, and continuing until the end, probably contributed largely to his untimely demise.

On graduating from the medical school of the University, he served what was called a continuous interne service in the Haverford Infirmary, but soon, having become interested in Otolaryngology, he is to be found working in the dispensaries of the Philadelphia Polyclinic and College for Graduates in Medicine under such eminent teachers as Drs. Packard, Watson, Gibb, Van Sant and Freeman, all Fellows of this College. Soon his work took him to other out-patient departments in the Children's, Mary Drexel, Lankenau (German Hospital as it was then called) and the University and Pennsylvania Hospitals, where he came under the influence and training of B. Alexander Randall and other masters in the field of otology and laryngology. In time he became otolaryngologist to the University, Lankenau, Children's and Mary Drexel Hospitals, and later still consultant to these well known and important institutions. He was a noted and able teacher and attained the grades of Assistant Professor of Otolaryngology and of Professor of Clinical Otolaryngology in the Medical School of the University and of Associate Professor in the Graduate School of Medicine. On reaching

*Read before the College of Physicians of Philadelphia, October 3, 1945.

the age of retirement in the Medical School, he was made Emeritus Professor of Clinical Otolaryngology, this being only the second time that this distinction had been awarded, the first having been when Dr. David Riesman became Emeritus Professor of Clinical Medicine. At the time of his death, he was still an active teacher in the Graduate School and, until his elevation to the presidency, he was a popular teacher for years in the instructional courses of the American Academy of Ophthalmology and Otolaryngology, which had made that organization unique among medical societies.

Dr. Babbitt's organizing ability was of a very high order and he was an invaluable and prominent member of many medical and lay groups. Among the latter were his two fraternities, Phi Gamma Delta and Alpha Mu Pi Omega and in both of these he was indefatigable in working for efficacy and economy and orderliness in their management. Their success in later years was largely due to his untiring efforts. In medical societies his interest was largely the same and he was but little interested in politics, never for himself. Of the many honors bestowed upon him by the national societies devoted to Otolaryngology, not one was ever sought by him. His good taste, good sense and innate modesty were all against any such thought. He had been a most efficient clerk of the Section on Otolaryngology of the College of Physicians of Philadelphia and later its chairman. The experience gained in these positions served him well when he became Secretary of the American Laryngological Association after having served as Treasurer for some years. Probably his chief duty in this office consisted in arranging the programmes for the annual meetings, always well done, and editing and publishing the yearly volume of Transactions. For this meritorious work he was elected President, universally regarded as the highest honor for an American laryngologist. A few years later, he became President of the American Laryngological, Rhinological and Otological Society and served on the Council of both of these important societies for four succeeding years. His last honor was his election to the presidency of the American Academy, after having served for years as necrologist, during which time he wrote memorials of probably hundreds of deceased fellows. He was also a valuable member of important Academy Committees, such as the Deafness Prevention Committee, both national and state, and the Committee for the establishment of a Pan-American Otolaryngological Congress, to which interest he devoted a large part of his presidential year. To further this object he undertook the study of Spanish. This Congress is in process of organization due to his efforts and those of our colleague Dr. C. L. Jackson. He was a Governor of the American College of Surgeons and was a Fellow of the American Otological Society to whose programmes he contributed many thoughtful articles.

Dr. Babbitt was a forceful, careful and scholarly writer on medical topics, having contributed chapters to three text-books and being the author of some fifty published articles, covering practically the whole field of his specialty. A glance over the titles shows his catholicity of interest, but in recent years his attention was devoted in large part to deafness prevention and amelioration and to geriatrics in relation to ear, nose and throat diseases. He was a member of the Editorial Boards of the Archives of Otolaryngology, of the Laryngoscope and of the Quarterly Review of Otolaryngological Literature, and Editor of five volumes of Transactions of the American Laryngological Association. Always interested in medical progress, he found time in his very busy life to conduct research in such subjects as Status lymphaticus, investigations into the causes of progressive deafness and otosclerosis, on labyrinthine reactions and the surgical cure of chronic suppurative otitis media. In this connection he devised a conservative operation for drainage of the attic, which in his hands proved eminently successful, in many instances producing dry ears after more conservative treatment had failed, and thus making the radical mastoid operation unnecessary He was a skillful surgeon, of conservative tendencies and of exceptional diagnostic ability. A fact that is probably known to few of his colleagues, and which the writer only learned a short time before his death, was that he had had rather extensive training and experience in general surgery and that while serving as a Major in the American Red Cross with the Service Unit of the Society of Friends in France in 1917–18, his work among the destitute French civilians caused him to perform many appendectomies and other general surgical procedures as well as the inevitable tonsillectomies and mastoidectomies. Having retired from active service at the Lankenau Hospital before the beginning of World War II, he was recalled to replace the two chiefs of service there, Drs. Edward Campbell and Robert J. Hunter, who were in the armed forces, and was later made chairman of the Hospital Staff

and Medical Director. He filled these posts in his usual conscientious manner, but this additional strain on his already overfilled time, probably contributed to his fatal illness more than an automobile accident in which he was involved.

Interest in athletics with him began in boyhood and continued unabated to the end. For years he had season football tickets at Franklin Field and attended the games regularly. During his Haverford teaching days he became President of the Middle Atlantic States Collegiate Athletic Association, which position he retained for six years and was for years a member of the National Football Rules Committee, which was a prime factor in developing the modern game of football, as we know it to-day. He was also chairman of the Central Board of Football Officials, whose duty it was, and is, to assign officials for the conduct of all intercollegiate matches, and this has largely done away with often unhealthy squabbling for advantage and produced more fair officiating and trained officials, as well as elimination of the unfit. Amateur sport owes him a debt of gratitude for his unselfish, honest and enlightened work in this field.

Dr. Babbitt enjoyed other fields of sport also, and rarely missed his summer trips for salmon fishing, at which he was an adept, in New Brunswick or for trout or bass in the Pocono Mountains. He was an enthusiastic member of the Doctors Golf Club and thoroughly enjoyed playing with his associates. He took great joy in his many professional and lay friendships and was constantly adding new friends to his host of old ones. He took keen pleasure in his social contacts at the Union League, the University and the Merion Cricket Clubs and his fraternities. A most loyal and lovable friend, he was always thinking of the other fellow rather than himself, and many a younger man will remember with lifelong gratitude the fatherly advice given and the helping hand extended in adversity or distress, or while endeavoring to gain a start in practice.

A keen student, a thoroughly competent surgeon, one of the most distinguished of American Otolaryngologists, a really great teacher, a splendid organizer and leader, a keen and fair sportsman, he believed in and lived by the Golden Rule, and his many friends throughout this great continent and in Europe will mourn his loss. Many of us will remember his favorite toast, which he attributed to his friend, the late Walter Camp.

We came into this world all naked and bare,
We live through this world in sorrow and care,
We go out of this world, God only knows where,
If we're thoroughbreds here, we'll be thoroughbreds there!

Dr. Babbitt was an accomplished musician and composed the song for the American Laryngological Association dedicated to his eminent fellow members, Dr. D. Bryson Delavan of New York, Dr. Harris P. Mosher, of Boston, and Dr. Chevalier Jackson, of Philadelphia. The singing of this song was a regular part of the programme of all of the annual dinners of the Association.

On June 20, 1921, Dr. Babbitt married Marcella Stovall Hardwick Cordray, who survives him as do his children, Mrs. Alan W. Hastings, Mrs. Edward L. Webster, Mary Adams, Mrs. Renwick McIver and Lt. David P. Cordray, M.C., U.S.N., who is a well trained otolaryngologist with promise of a brilliant future after the completion of his military service.

Although the author of many papers, monographs and chapters in textbooks, all of value, perhaps Dr. Babbitt's chief service to otolaryngology lay in his indefatigable work and organizing ability. No task was too hard for him and he gave freely of his time, energy and resources. No more pleasant companion than Jim Babbitt ever lived, no truer or more loyal and unselfish friend. He felt a keen friendship for the members of this College and of the other organizations with which he was connected and would have done anything possible for their welfare, even though he knew them not personally. He was a strong character and the College loses one whom it cannot readily spare for his term of usefulness was by no means past.

TRANSACTIONS & STUDIES

*of the*

College of Physicians of Philadelphia

Volume 13
(Fourth Series)

Number 4
(February 1946)

# Address of the Retiring President*

*By* O. H. PERRY PEPPER

THE College of Physicians of Philadelphia has come through the war years in truly excellent health. Inevitably, the activities of the College during the war years were, to a large measure, in the nature of a holding operation, but more advances were made than might have been anticipated; and your President is proud to report that no retreats were made, either material or spiritual. The truth of these statements is documented in the annual reports of Officers, Committees and Sections which as usual appear in the *Transactions*.

Our membership has increased, the use of the library has widened and the attendance at the scientific meetings has been gratifying. A further word about each of these items is indicated.

Death, during the past year, has taken from the College the following Fellows whose names will be read as the College stands silent in their memory:

*Resident Fellows*†

Robert S. Alston
Bernard I. Comroe
Edward Blanchard Hodge
William Hamilton Jefferys
Roland N. Klemmer
Joseph McFarland
Henry Alexander Miller
Josef B. Nylin
Harold D. Palmer
George S. de Renyi
William John Ryan
J. Clinton Starbuck
Edward Q. Thornton

*Non-Resident Fellow*†

W. P. Conaway

Of these memoirs of the following will be found in the *Transactions:*—Edward B. Hodge‡; Joseph McFarland.[1]

Fellows to the number of thirty-three have been elected to fill our ranks.

Our great library is being used increasingly and this is proper and must be encouraged—an unused library is dead. With the greater activity in research of commercial firms their use of our library for reference is also greater and it is gratifying to report a beginning appreciation on their part of their obligation to us for this service by financial contribution to our library.

During the war years our College and the Philadelphia County Medical Society have held joint scientific meetings with great success and a resulting closer amity of the two organizations. In spite of this, it is the opinion of your retiring President that the College should return to the pre-war custom of holding its own series of scientific lecture meetings. At the same time, every effort should be made to maintain friendly relations with the County Society and to further

* Prepared for the Business Meeting of the College, January 9, 1946.

† For dates, see necrological list, p. 180.

‡ See p. 147, this issue.

[1] To be published.

the cooperative efforts of the two in other matters such as those of civic interest and of public health.

Of the Fellows who entered the Armed Forces, almost one-half have returned and it is to be expected that the others will follow soon. Already the return of these Fellows to a full dues-paying status has helped to balance our fiscal budget. No individuals have entered our Army and Navy at a greater sacrifice than the doctors, the vast majority of whom were not members of a firm or group to continue their work and income. The College is deeply sensible of the willing contribution of these officers to the war effort. One of the duties handed on to the incoming College administration is the arranging for some function in honor of our Fellows who served in Army and Navy, after all have returned.

Other matters which the war forced the College to postpone and which are handed on to the new Officers and Council include a review of the criteria for Fellowship including perhaps the certification by an appropriate American Board and the question of how the College can further its service to the community and to national medicine and health. Involved in this question is the problem of the time-consuming duties of the Secretary of the College. His work is many times more than that of any other officer, councillor or committeeman; if it were not for the wisdom and the generous gift of time and effort by such a man as Dr. J. Harold Austin, the College would not function efficiently. Years are required to gain all the detailed information needed by the Secretary and it is too much to ask of any Fellow. If the College is to increase its activities in any of the several directions in which it might well serve, this will be possible only if additional salaried personnel is employed including perhaps a full-time medical secretary.

In relinquishing the office of President, I wish to assure the Fellowship of my appreciation of the opportunity to serve the College and to thank the many Fellows who in various capacities have carried the burden during the past three years. I wish to express my deep sorrow, both personal and official, that Vice-President Edward B. Hodge did not live to succeed to the Presidency and at the same time I congratulate Dr. J. Parsons Schaeffer and Dr. T. Grier Miller on their selection by the Fellowship for their new offices. In closing, let me repeat from my report of last year that I feel a mixture of pride in what has been done under adverse conditions and of disappointment that some greater advances could not be achieved.

# Address of the Incoming President*

*By* J. PARSONS SCHAEFFER

ON the occasion of assuming the duties and responsibilities of the presidency of the College of Physicians of Philadelphia, I am not unmindful of the great honor which comes to me at this time. Especially do I feel honored when I recall the distinguished and outstanding physicians who served in the capacity of president in the immediate and the more distant past. I am grateful to the members of Council and the Fellows of the College for the confidence they have placed in me in making it possible to be included with this group.

As I contemplate the many and varied responsibilities of the office of president, it would appear that the position merits more time and ability than I can possibly bring to the task. Probably some other Fellow should have been chosen in my stead. I am, however, fully appreciative of the needs and the work entailed and I shall put forth my best effort in serving the College. More than this, I cannot promise. Then, too, I shall look forward to have the advice and cooperation of a number of Ex-Presidents, the decisions and direction of Council are, of course, required, and the help of the Elective and Appointive Committees will serve to lighten the load of the president. Fortunately, I have had the opportunity and pleasure of serving on certain Standing Committees of the College during the incumbencies of five presidents and serving on Council during the terms of four presidents. I can truthfully say that I enjoyed my work in these capacities and I feel that these contacts should prove helpful to me now. The continuance in office of Dr. Austin, who has served the College in an efficient manner for many years, is gratifying to me.

As I take on the duties of president, I recognize the long and honorable history and the rich traditions of this College. The activities of the College have favorably influenced not only Philadelphia medicine but that of the nation as well. The Fellows of the College should resolve that this influence shall not only be maintained but be strengthened. My feeling is that the College of Physicians should be the very leaven of medicine in this community. In saying this, I realize that the College is not and cannot be self-contained nor self-sufficient and that on occasions it is manifestly advantageous to invite others from the outside to participate in programs. The College must also always assume the right to move into and to utilize related and cognate fields of science in the performance of its varied functions. In all of these aspects our opportunities and responsibilities are equally great.

I believe that Fellowship in the College should only go to men who are fully qualified for membership. It should be considered an honor to become a Fellow of the College of Physicians. In nominating men, Fellows of the College should sense their responsibility with reference to worthiness and fitness of candidates. There are, doubtless, a number of physicians, not now members of the College, who merit consideration for Fellowship. Occasionally certain younger men would qualify if a few additional years were allowed to intervene between graduation and nomination for membership in the College. This longer interval period would enable the individuals to complete certain researches or give them more time in other ways to qualify.

There was a time when I felt that Fellowship should only go to men who, through research and publications, contributed to the furtherance of scientific medicine. I still hold to the principle of high standards for admission to the College of Physicians, but I have come to believe that Fellowship should on occasions be granted to those who have been active in the public service, to those who have given much of their time and ability in the furtherance of legislation becoming the best interests of medicine, and at times to men in the general practice of medicine or special fields who have done outstanding work and merit recognition for it. In other words, I have come to the belief that there are a number of ways in which a physician may qualify for Fellowship in the College of Physicians. Clearly, however, the responsibility in bringing worthy men into the Fellowship of the College rests not only with

* Jan. 9, 1946.

Council but with the entire Fellowship of the College.

During the troublesome times of World War II the College of Physicians of Philadelphia and the Philadelphia County Medical Society united their efforts in the interests of scientific programs. The scientific lectures were given alternately at the College of Physicians and the Philadelphia County Medical Society. This practice is in force at the present time and will be until the occasion of the Thomas Dent Mütter Lecture in April, 1946. When the matter of joint meetings was first presented to Council, I felt that it was a mistake and believed that both the College of Physicians and the County Medical Society should continue their individual scientific programs. At the time, however, the opposite opinion prevailed with the result that the College and the County Medical Society provided for combined scientific lectures. As time went on I began to look upon the arrangement in a different light and came to believe that it was a good thing. I felt that a helpful and coordinating spirit came into being between the College and the County Society. In view of these observations I am hopeful that the combined effort may be continued, at least, for another year. Whether or not the College of Physicians should then return to its individual program is a matter for future decision. It may be argued that both the College of Physicians and the County Medical Society have peculiarly individual and varied functions to perform and that if too much time is consumed in a common effort the real purposes and needs of the individual institution and society will be neglected and remain undone.

I was greatly interested in the report of Dr. Starr, the treasurer, and was pleased to note the financial status of the College and that we shall be privileged to move into the new year hopeful that we shall be enabled to meet the budget commitments. No one can foresee what the financial situation will be a year from now, but my feeling is that it would be folly to become unduly alarmed at this time. Bridges must, however, be crossed when we find it necessary to do so.

# Memoir of Edward B. Hodge*

*By* CHARLES J. HATFIELD

THE death of Dr. Edward Blanchard Hodge on June 19, 1945 was a severe loss to many Medical organizations, and to a vast number of personal friends. He was a man of distinguished ability and of a high grade of personality, that was marked by faithful service to all colleagues and all friends with whom he was associated.

Born August 21, 1875, the son of very distinguished parents, he seems to have accomplished fine work at home, in school, in College and in the University! In every Hospital on whose surgical staff he served, including our Children's Hospital, the Pennsylvania, the Presbyterian, the Germantown, and the Chester County Hospital in West Chester, he made a fine record. His membership in the College of Physicians of Philadelphia for many years was so much appreciated that he became Vice-President several years before his death.

Recognition of his great ability, fine character and most attractive personality was demonstrated in all places where he dwelt. He was a trustee of Princeton University, also of the Princeton Theological Seminary, of our Children's Hospital, the Children's Seashore House of Atlantic City, and a member of the Board of Directors of the S. E. Pennsylvania Chapter of the American Red Cross, where he was a Technical Supervisor of the Blood Donor Center. In many other patriotic organizations he was a valued member. In World War I, he was at first a Captain in the Army Medical Corps, and served for years overseas, being promoted to Commanding Officer of Mobile Hospital, No. 8, and was soon commissioned as a Lieutenant-Colonel.

Dr. Hodge's services in the field of Medicine were valuable. However, his fine character and wonderful personality made the sorrow of his death an affliction to all the hundreds of non-medical individuals who had been fortunate in being associated with him!

Surely, we, as members of the College of Physicians of Philadelphia, are very anxious to have a memoir of our distinguished colleague and dead friend, Dr. Edward B. Hodge, for inclusion in the historical records of the College.

* Prepared and published by direction of the Council of the College.

# Annual Report on the Library*

In our report for the library year 1940–41 we wrote: "When the war is over, there will be time and reason to review its effect upon the library." The war is not yet over, either technically or actually; furthermore, its effects will be felt for years after its official end. And yet we are, in a large sense, again at peace. Our communications with the rest of the world are being rapidly restored; faces long missed from our rooms are again gratefully to be seen. It is time, and there is some reason, for at least a tentative, interim review of the effects of the war upon the library. In attempting one at this time, we have especially in mind our returning Fellows and other readers who so frequently express an interest in learning how the library has fared during the war. With but little accent on the year just past, this report is chiefly for them.

## Periodicals

At the outbreak of the European phase of the war in 1939, the library was regularly receiving 1,202 periodicals. In 1942, this figure had dropped to its wartime low of 670. All new major medical periodicals in the English language have been added immediately on publication, and additions have been made in the Latin American field. The present report puts the number of periodicals currently received at 899, which includes some of the European ones whose shipment was held up during the war.

Our European subscriptions (except the Italian) had for some years been handled by an agency in Amsterdam. This proved to be exceedingly fortunate for us in two respects. The agency was able to make shipments to us up to the very moment of our entry into the war; it was able to collect the journals for us from then on—and its warehouses escaped bombing. Thus we may look forward to having files, at least of the non-Italian periodicals, ultimately as little broken as seems humanly possible.

Our Italian subscriptions were handled by an agency in Rome. There the picture seems not quite so bright, though we have reason to hope that files for at least the earlier years of the war are being held for us.

The British periodicals were received with astonishing regularity straight through the war, though there are a few gaps created by enemy action at sea and the unavailability of replacement copies.

What *Ersatz* methods of obtaining the enemy and neutral material during the war did we have? Copies were getting to this country and being indexed—which means that the material was in demand by our readers. There was formed a Joint Committee on Importations which allocated to subscribing libraries the few journals which, with Government aid, it was able to get into the country. We presented what was admitted to be a strong case for a high priority in this distribution —and got nothing, presumably on the basis of our close proximity to Washington and New York. The Alien Property Custodian authorized the reprinting of certain of the basic Axis-controlled periodicals from unique copies located in this country (we loaned a volume of *Biochemische Zeitschrift* for this purpose), and we subscribed to those we were accustomed to receive, believing that, should we be fortunate enough to find the originals available to us after the war, the reprints would still be in demand by libraries less fortunate. Meanwhile, at the Library of Congress there was developed a checklist which, supplemented by information in the hands of the Joint Committee, located individual wartime numbers of the Axis periodicals held in this country. To all this pooling of information and coöperative effort this library contributed its bit.

Unexpectedly favorable as the situation appears to be in respect of the foreign periodicals, complete success in restoring the files with original copies is scarcely to be hoped for. There were some losses, by enemy action at sea and by other means, which cannot be recovered in the original form, owing to the very restricted number of copies published; but thanks to microfilm, the photostat, and a more highly developed system of interlibrary communication and coöperation, there should be few gaps which cannot be filled in one way or another—provided the necessary funds be forthcoming.

## Books

The importation of European books of course also stopped during the war. Again the Alien

* Oct. 16, 1944–Oct. 31, 1945.

Property Custodian came to the rescue in some measure. Of those authorized for reprinting, we purchased such as we would normally have purchased in the original. A few additional books were obtained through bookdealers' catalogues. On the whole, however, we must regard the restoration of our collection in this respect as one of our major problems. Some help may be expected from our Netherlands agency, which is prepared to suggest the important European books of the war years that are available for purchase. In our *Booklist* we are urging the Fellows and other users of the library to recommend promptly foreign books that they would like to have available in the library. That request is repeated here.

### Use of the Library

*Attendance.* In 1940, after a steady climb for some years, attendance in the library had reached a peak of 13,485. By 1943, the war had reduced the number of visitors to 7,759. In 1944, the trend was reversed, the attendance jumping to 9,016. The figure for the current year, 10,367, along with the general situation, indicates a steady advance along the road back to the pre-war figure. Most noticeable during the war was the altered use of the library by the readers; few spent long hours or days with us surrounded by multitudes of volumes, as formerly; it was 'shot-gun' reading for the most part.

*Circulation of Volumes.* Reduced attendance inevitably brought in its wake reduced circulation of the volumes. In 1940, 8,379 volumes were taken out of the library; by 1943, the number had dropped to 5,319. A slight recovery was noted the next year (5,707); a more marked one in the year just passed (6,664). The low watermark in use of volumes in the library was not reached until 1944, when the number had declined to 29,077 from the peak of 50,520 in 1940. The present report, putting the 1945 figure at 30,075, indicates that here, too, the corner has been turned.

*Photostat: Inter-library Loan.* Reduced attendance and circulation of material are, of course, natural effects of war visited upon almost all libraries. We would have felt out of it indeed, had the library's services to the war effort stopped there—but they did not. It is likely that some of our most useful services were performed for persons who have never yet set foot in the library.

As indicated above, we were singularly fortunate in having received from Europe later published material than seemed to be available elsewhere in the country; our holdings in this material were registered with the checklist at the library of Congress. The new edition of the *Union List of Serials*, appearing in 1943, for the first time let the scholarly world in on the secret of just how rich our collection of serial publications is, thus amplifying the information on our collections already available at the Philadelphia Union Library Catalogue. The result was that we received numberless requests for loans and photostats of rare, sometimes elsewhere unavailable, material from Departments of the Federal Government, war agencies, commercial organizations engaged in experimental work for the Government, and many other bodies to which our name was doubtless unknown before the war. The wise and liberal policy of the Library Committee encouraged us to meet every demand of this sort that we could. A measure of this activity is to be had in a comparison of the pre-war and last-year-of-the-war figures on the inter-library loan and use of the photostat service. In 1940, we sent 117 volumes out on inter-library loan to 25 libraries—in 1945, 1,099 volumes to 67 libraries, the majority of which, of course, were non-medical. In 1940, 1,470 photostatic prints were supplied—in 1945, 2,828. Thus our returning Fellows have the assurance that, though the library, like most others, suffered a diminution in intramural use during the war, it nevertheless made the contribution to the war effort that it was best equipped to make, one without precedent, we believe, in its long history.

### Personnel

Readers returning after several years' absence will find the visual aspects of our reading rooms little changed except in one particular—the features of those now ministering to their needs they will find, at first, largely, perhaps completely, unfamiliar. For one of the effects of the war on the library is that, of the seven assistants on duty at the outbreak of the war, only one now answers the roll call. Our wartime reports go into this matter in some detail, and the present staff is named below; let is suffice here, therefore, to express the hope and belief that the warm friendliness that characterized the relations of readers and staff before the war will quickly reestablish itself—not forgetful of those no longer

with us, but sensible of such compensations as the gods have vouchsafed us.

### The Past Year

A word or two, for the record, on the year covered by the following statistics.

One of the several indexes useful in determining the general regard in which a library is held is the number of those who make voluntary donations of one sort or another to it. In this respect, our library has always been singularly fortunate. It is gratifying to note, therefore, that the number of donors in the past year (282) was greater than that of any of the earlier war years and very nearly reached the 1940 figure (290). The number is too large, obviously, for us to itemize the specific donations and comment on the more outstanding ones, as we would like to do; but we cannot let this occasion pass without a special word of gratitude to these kind and real "friends of the library."

Again it is our pleasure to acknowledge a very serviceable grant of $1,000 from the Smith, Kline & French Laboratories, through Mr. Theodore Wallace, made, on the initiative of our Fellow Dr. William L. Long, in generous recognition of the library's considerable services to the laboratories. Few but the library administration realize, probably, what extensive use of the library is made by a number of such concerns; and it is gratifying to be able to put on record our appreciation of the recognition thus accorded the library by one of these concerns.

The Library Committee and the librarian wish to express their appreciation of the continuing and contagious enthusiasm brought by Dr. Samuel B. Sturgis to his work on the medical art collections. Despite many obstacles, he has carried on this work as best his time permitted. In like manner, Dr. William N. Bradley has continued work on the Bradley Collection and greatly enriched both it and the Sturgis Collection during the year.

Two exhibits that attracted more than passing attention may be mentioned: 1) that on the 1943 and 1944 Nobel prize winners in medicine and physiology; 2) the medical art show sponsored by the magazine *Modern Medicine*.

*The Staff.* In January, 1944, we lost two valuable members of our staff: Miss Ruth Yarger, assistant cataloguer; and Miss Concetta Ciotti, page. We were fortunate in obtaining as immediate replacements, Miss Gwen MacMurray, for Miss Yarger's position; Miss Anne Ludovici, for Miss Ciotti's. Gaining a husband, but not deserting us for him, Miss Mary Mars, photostat operator and page, will hereinafter be referred to as Mrs. Bliss.

After a successful year as chairman of the membership committee of the Special Libaries Council, Miss Manson was appointed chairman of its program committee. With exceptional industry, she accomplished much in the way of re-arranging and cataloguing valuable, hitherto ill-treated material, and was a tower of strength to all of us. Her signal contribution to the library's welfare was gratefully acknowledged when the Library Committee, on the librarian's recommendation, bestowed on her, on June 1, 1945, the additional title of assistant librarian. Of each member of the staff, indeed, it would be easy to recount some pleasantly remembered evidence of special skill or good-will.

The librarian served a second term as president of the Philadelphia Metropolitan Library Council and continued as secretary of the American Association of the History of Medicine. As delegate of the History of Science Society, he attended the meetings of the American Council of Learned Societies in Boston; and as delegate of the Medical Library Association attended meetings of the Joint Committee on Books for War Devastated Areas, in New York. In November, 1944, he read a paper (unpublished) before a joint meeting of the Section on Medical History of the New York Academy of Medicine and the New York Society for Medical History. In October, 1945, he read a paper before the Biological Section of the Washington, D. C., chapter of the Special Libraries Association. He continued to serve as editor of the College's *Transactions & Studies* and as secretary of the Hall Committee.

For the convenience of returning Fellows, the names and positions of the present members of the staff are given below. Readers familiar with the library know, however, that stations are filled for relief periods by another member of the staff than the title-holder.

*Assistant Librarian and Cataloguer*

Miss Clara S. Manson

*Assistant in Charge of the Reading Room*

Mrs. Mary Elizabeth Shaffer

*Assistant in Charge of the Periodicals Room*

Mrs. Elizabeth Bready

*Assistant Cataloguer*

Miss Gwen MacMurray

*Secretary to the Librarian, and General Assistant*

Miss Kathryn Haegele

*Photostat Operator and Page*

Mrs. Mary E. Bliss

*Page*

Miss Anne Ludovici

## Inventory

| | 1945 | 1944 | |
|---|---|---|---|
| *Total number of accessioned[1] items* | | 163,025 | 161,740 |
| | 1945 | 1944 | |
| Incunabula | 415 | 415 | |
| Manuscripts (including a few typescripts) | 638 | 634 | |
| Other items | 161,972 | 160,691 | |
| | 163,025 | 161,740 | |
| *Total number of unaccessioned[2] items* | | 322,180 | 318,353 |
| Reports and Transactions (annual or occasional) | 25,879 | 25,819 | |
| Periodicals "reserve"[3] | 5,209 | 4,701 | |
| Complete and incomplete volumes of other periodicals not regularly received | 5,133 | 2,673 | |
| Theses and Dissertations | 48,582 | 48,273 | |
| Pamphlets (fewer than 100 pages) | 237,377 | 236,887 | |
| | 322,180 | 318,353 | |
| Total number of current periodical publications regularly received | | 899 | 724 |
| Portraits[4] | | 62,662 | 60,822 |

## Distribution of This Material

| | Accessioned Items | Unaccessioned Items |
|---|---|---|
| General Library (including the Lewis Library) | 158,797 | 322,176 |
| On permanent deposit: | | |
| Gross Library | 3,811 | 4 |
| Parry Library of the Obstetrical Society of Philadelphia | 217 | 0 |
| Mütter Museum[5] | 200 | 0 |
| | 163,025 | 322,180 |

[1] An accessioned item may be any kind of material that is kept within covers, whether these be made commercially or in the library, of paper or of more durable material. The accessioned item might comprise, for instance, part of a book, or one or more books; a part of a periodical volume, or one or more complete volumes; reports, pamphlets, or theses, single or collected; an atlas or photograph album, collection of correspondence, etc.

[2] While the accessioned items contain some material in paper covers, it should be noted that most Reports and Transactions, pamphlets, and theses, also paper-covered, are not accessioned, but that any of them might be, if any intrinsic reason for so doing should present itself.

[3] More-or-less complete duplicate volumes of important and much-used periodicals.

[4] Including 112 oil, and 471 other, framed portraits in the care of the Committee on College Collections. The count of portraits represents the number of entries on the cards in the portrait catalogue. The entries represent, in turn, both loose portraits and those in books, many of them, of course, being merely different reproductions of a single original. It does not include the approximately 2,800 photographs in the Bradley Collection, nor hundreds of portraits in the Sturgis Collection, now in process of being catalogued.

[5] The books of the Mütter Museum are not permitted to be removed from the College building.

## Current Periodicals

(Census by country)

| Country | Purchased | Exchanged | Gratis | Annuals | Total |
|---|---|---|---|---|---|
| North America | | | | | |
| Canada | 1 | 8 | 9 | 2 | 20 |
| U. S. A. | 223 | 77 | 225 | 45 | 570 |
| Latin America | | | | | |
| Argentina | 10 | 11 | 10 | | 31 |
| Brazil | 5 | 15 | 6 | | 26 |
| Chile | | 3 | 2 | | 5 |
| Colombia | | | 1 | | 1 |
| Peru | | 1 | 1 | | 2 |
| Uruguay | | 5 | 2 | | 7 |
| Venezuela | 1 | | 2 | | 3 |
| Guatemala | | | 2 | | 2 |
| Mexico | 2 | 6 | 5 | | 13 |
| Cuba | 1 | 7 | 8 | | 16 |
| Haiti | | | 1 | | 1 |
| Jamaica | | | 1 | | 1 |
| Puerto Rico | | 1 | | | 1 |
| Trinidad | | | 1 | | 1 |
| Europe | | | | | |
| Eire | 1 | | | | 1 |
| France | 9 | | 1 | | 10 |
| Germany (APC)* | 20 | | | | 20 |
| Gt. Brit. | | | | | |
| England | 73 | 13 | 11 | 3 | 100 |
| North Ireland | | 1 | | | 1 |
| Scotland | 2 | | | | 2 |
| Portugal | | 1 | | | 1 |
| Russia | 11 | | | | 11 |
| Scandinavia | | 4 | 1 | | 5 |
| Spain | | 2 | | | 2 |
| Switzerland | 21 | | | | 21 |
| Near East | | | | | |
| Egypt | | 2 | | | 2 |
| Palestine | 2 | | | | 2 |
| Syria | | | 1 | | 1 |
| Africa | | | | | |
| British | 1 | 2 | | 2 | 4 |
| French | 1 | 1 | | | 2 |
| Asia | | | | | |
| Ceylon & India | 3 | 4 | 1 | | 8 |
| Pacific Area | | | | | |
| Australia & New Zealand | 1 | 2 | 1 | | 4 |
| Hawaii | 2 | | | | 2 |
| Totals, 1945 | 390 | 166 | 292 | 51 | 899 |
| Annuals | 25 | 7 | 19 | 51 | |
| Grand Totals, 1945 | 415 | 173 | 311 | | 899 |
| Grand Totals, 1944 | 327 | 161 | 267 | | 755 |
| Grand Totals, 1939 | 688 | 248 | 266 | | 1,202 |

* Reprints published in this country under the auspices of the Alien Property Custodian.

*Foreign titles:* The V-days each brought a revival in our foreign list. Slowly but increasingly the foreign shelves are filling up again. Of the returning neutrals, Scandinavia, Spain, Palestine and Egypt reappear. And out of the war emerge Russia, France, each with titles which we have not seen for many a long year. As usual, our neighbors in Latin America have sent through the greatest number of journals, and this year, with greatly increased regularity. Switzerland has stepped up its shipments likewise.

*New titles:* A total of 84 periodicals were added to the Norris Room in 1944–45 (83 journals, 1 annual). 31 of these were purchased, 20 received in exchange, and 33 came in as gifts. There were 19 that began with volume one; and 7 commenced publication in 1945.

*Separate Issues* received, checked-in on cards, and shelved numbered 7,257. Duplicates presented by Fellows, etc., equalled 9,912; Reserves, 508.

*Visitors* to the Norris Room for the year totaled 5,190.

## Readers' Use of the Library

*Library hours:* Through the fall, winter, and spring, the library was open weekdays, except Wednesdays, from 9:30 to 6; on Wednesdays, from 1 to 9:30. During the summer, the Wednesday schedule was retained but the library was closed on Saturdays, and on the other weekdays was open from 9 to 5. The schedule for the early fall of 1945, the last period covered by this report, was the same as for the first period designated above; on Oct. 22d, however, the closing on weekdays other than Wednesday was advanced to 5:30. The following legal holidays were observed by the library: Thanksgiving, Christmas, New Year's (in the cases of the last two, from 1 p. m. on the preceding Saturdays), and Labor, Days. The library was also closed on the national day of mourning following President Roosevelt's death and during the two-day observance of V-J Day.

*Number of Visitors:*

| | 1945 | 1944 | Totals 1945 | Totals 1944 |
|---|---|---|---|---|
| Days (including evenings) | (303) | (302) | 10,367 | 9,016 |

*Circulation of books:*

| | 1945 | 1944 |
|---|---|---|
| Number of volumes taken out | 6,664 | 5,707 |
| (Books: 3,168; Periodicals: 3,595) | | |
| Number of volumes consulted in the library[6] | 30,075 | 29,077 |

*Inter-library loans:* The library has sent 1,099 (1944: 267) volumes on inter-library loan to 67 (1944: 55) libraries in 15 (1944: 13) States and has borrowed 30 (1944: 17) volumes from 15 (1944: 6) libraries. There were, as happens each year, a number of requests we could not fill; 24 volumes asked for we did not have; 32 were on the restricted list; 39 requests were for current unbound journals. Our photostat answered the need in some of these cases, and in many more a knowledge of this service obviously forestalled a request for loan of a volume.

*Photostats:* 2,828 photostatic prints were furnished on request (1944: 2,212); 67 prints to the library (1944: 263).

## Acquisitions and Accessions

*Received from all sources:*[7]

*1945:* 1,344 volumes (including the bound and accessioned volumes of periodicals, 60 unbound reports); 1,096 pamphlets; 661 theses; 18,574 numbers of various journals.

*1944:* 1,057 volumes (including the bound and accessioned volumes of periodicals, 33 unbound reports and 45 duplicates); 615 pamphlets; 577 theses; 5,340 numbers of various journals.

*Accessions:*

*1945:* 1,285 volumes (775 by purchase; 374 by gift; 136 by exchange). (Books, 612; Periodicals, 673).

*1944:* 979 volumes (586 by purchase; 316 by gift; 77 by exchange). (Books, 539; Periodicals, 440).

## Donations

The individual donors for the past year number 282 (1944: 216). The library is indebted for large gifts of books, pamphlets, and unbound periodicals to the following donors:

P. Blakiston & Co.; Boston Medical Library; F. A. Davis Co.; Miss J. Eshner; Evans Dental Institute; Drs. J. C. Gittings, E. Halpin; Institute of Experimental

[6] The number of volumes "consulted in the library" includes only those supplied on demand. Readers have access to the bound volumes of periodicals and reference works kept on the shelves in the Reading Room; the Fellows, and occasionally others, by special permission, have access to the book-stacks. There are, therefore, many volumes consulted of which no accurate record can be kept.

[7] As usual, not all the pamphlets, theses, and numbers of various journals listed as received had been checked for keeping or discard at the close of the library year.

Biology of the University of California; Drs. C. L. Jackson, E. B. Krumbhaar; Lea & Febiger; J. B. Lippincott Co.; Medical Library Exchange; Merck Institute for Therapeutic Research; Drs. H. H. Morris, G. P. Muller, F. R. Packard; Rockefeller Foundation; W.B. Saunders Co.; South African Institute for Medical Research; Drs. A. A. Stevens, J. M. Swan, L. M. Tocantins, J. Walsh, H. C. Wood; Wyeth, Inc.; Dr. W. Zentmayer.

Various publishing houses have presented volumes as follows: P. Blakiston's Son & Co., 3; F. A. Davis Co., 7; Lea & Febiger, 15; J. B. Lippincott Co., 31; W. B. Saunders Co., 47.

Other individual donors were as follows: Drs. F. H. Allen, H. L. Arnold, Jr., L. Averett; Mr. J. R. Bahl; Drs. W. S. Bainbridge, R. J. Behan, N. Blumberg; S. W. Boggs; Drs. W. G. Bowerman, W. N. Bradley, S. Bradbury; G. Branco; Drs. C. C. Burlingame, T. S. Cullen, Mrs. E. R. Cunningham; Drs. W. A. N. Dorland, L. Edelstein; Mr. J. T. Emlen; Dr. H. Freed; M. M. Friedman; Drs. J. Fulton, P. M. Groedel, S. McC. Hamill; Mr. J. L. Haney; Drs. A. E. Hertzler, W. Hewson, G. Hinsdale; Capt. R. C. Holcomb; Dr. A. C. Jacobson; Capt. T. E. Keys; Mr. P. O. Kristeller; Drs. W. G. Leaman, Jr., E. G. Martin, M. McCutcheon; Mr. W. B. McDaniel, 2d; Drs. E. H. McCavack, E. J. Morris, S. Mudd; Miss M. Naylor; Drs. C. C. Pierce, C. Proskauer, M. H. Rea, P. Q. Roche, H. Roesler, H. C. Ruche; Miss M. S. Rukeyser; Drs. O. Saphir, P. J. Sartain (bequest), L. C. Scheffey, D. Schwimmer, T. H. Shastid, R. P. Strong, H. Swanberg, M. Thorek, J. M. Thorington, G. Tugendreich, E. Urbach, C. A. Volf, C. Watson, C. E. Watson.

### Exchanges

The *Transactions & Studies* was sent, either as gift or in exchange, to 297 organizations.

The library has received 1,066 issues of journals through the Medical Library Association Exchange.

Theses and dissertations to the number of 161 have been received on exchange from the following European school of medicine; University of Paris.

### Work of the Cataloguers

| | *1945* | *1944* |
|---|---|---|
| Accessioned items catalogued or recatalogued | 833 | 790 |
| Unaccessioned pamphlets and Fellows' reprints catalogued by author or by author and subject | 1,530 | 1,681 |
| Reprints (from journals not in the library) entered under the name of the journal (periodicals catalogue) | 46 | 97 |
| Cards typewritten, examined and filed | 14,219 | 14,582 |
| Cards revised, typewritten, examined and filed | 3,601 | 3,377 |

W. B. McDaniel, 2d
*Librarian*

Approved:
Burton Chance
*Chairman*

# Annual Reports of the Committees of the Mütter Museum and College Collections

## The Museum

*Changes in Committee Personnel.* The death of the Honorary Curator, Dr. Joseph McFarland, deprived us of one whose comments and suggestions were a great help. Dr. McFarland further gave the Museum favorable notice by his several published accounts of items in the Museum.

Dr. J. Parsons Schaeffer resigned from the committee due to his being chosen as Vice-President of the College. Dr. Schaeffer was the senior member of the Committee and chairman. His long experience with the routine of the committee and regulations of the College made for the efficiency of the Museum. It will be difficult for anyone to handle the affairs of the committee as expertly as did Dr. Schaeffer.

*Activities.* The museum was open weekdays from 10–1 and 2–6 except on Wednesdays when the hours were from 1-6 and Saturdays, 9:30–1. In addition the Museum was open on the evenings of the Stated Meetings of the College and at some Sectional Meetings when the interest seemed to warrant it.

There were 765 visitors during the year.

The fifty-seventh Thomas Dent Mütter Lecture was given by Stanley P. Reimann, M.D., Director of the Research Institute of the Lankenau Hospital and Professor of Oncology, Hahnemann Medical College, who spoke on "The Cancer Problem As It Stands Today." This lecture was printed in the *Transactions & Studies* of the College, April 1945 issue.

During the year the late Dr. Joseph McFarland, Honorary Curator of the Mütter Museum wrote a paper on Dr. Harrison Allen's thoracograph, entitled "That Infernal Machine." This appears in the *Transactions & Studies* of the College, April 1945.

A paper on "Letters from Professor Hyrtl Found in a Mütter Museum Scrapbook" was written by Mrs. Ella N. Wade, curator. It appeared in *Transactions & Studies* of the College, December 1944.

Dr. Pemberton again used the specimens in the Museum to illustrate lesions of arthritis and ankylosis.

Dr. Joseph McFarland was again appointed Honorary Curator of the Mütter Museum and Mrs. Ella. N. Wade Curator and Clerk-technician, for the year 1944-45.

*Accessions.* Accessions to the permanent collection of the Museum, during the year, and subject to the Mütter Deed of Gift, were as follows:

Presented by *Dr. Edward B. Hodge:*

Pocket case of instruments
Set of apothecaries' scales

These instruments formerly belonged to Dr. Hugh Lenox Hodge who was Professor of Obstetrics at the University of Pennsylvania from 1835 until 1863.

Presented by *Dr. G. N. J. Sommer* of Trenton, New Jersey:

Scarificator with twelve blades
Spring lancet
Set of Weights

Presented by *Miss Harriet Sartain* from the Estate of Dr. Paul Sartain:

*Eye Instruments:*

1 pair of Pfund glasses to absorb heat
1 DeWecker's iris scissors
1 combination eye lancet and scoop
1 Jäger lid plate
1 Theobold's lachrymal probe

*Aural Instruments:*

1 set of aural instruments (after Politzer)
2 eustachian catheters
1 Blake's ear snare
2 ear probes
2 ear applicators
1 raspatory for mastoid operation
1 gouge for mastoid operation

*Nasal Instruments:*

1 Bosworth's nasal snare
1 Jarvis' nasal snare
3 adenoid curettes (assorted sizes)
1 Cohen's post nasal cutting forceps
1 post nasal forceps
1 nasal saw
1 Bosworth nasal speculum
1 nasal packer
3 nasal applicators

*Laryngeal Instruments:*
Set of 3 Mackenzie's Tonsillotomes
1 Mathieu Tonsillotome
2 tonsil scissors
1 Wood's Uvula scissors
1 box laryngoscopic mirrors
Michel's laryngoscopic mirror
Priestley Smith's candle lamp
Stethoscope (Da Costa's)
Insufflator for larynx
Tonsil tenaculum forceps
Tonsil hook
Laryngeal applicator
2 laryngeal brushes
1 finger guard
1 Tonsil hemostat
1 Heister's mouth gag
1 mouth gag
1 Turc's tongue depressor

*Instruments for other uses:*
1 Molesworth dilator
1 Demarquai's anal speculum and dilator
1 glass syringe for large doses of antitoxin
1 small glass hypodermic syringe

There were many duplicate instruments in this collection which are stored for future use or for exchange.

## The College Collections

*Accessions*

Presented by *Dr. William Zentmayer:*
A collection of badges and buttons of International Ophthalmological Congresses and Medical Societies.

Presented by *Dr. Burton Chance:*
Early Singhalese physician's dagger and stylus, used for cutting palm leaves and writing on the prepared leaves (Ola) of the talipot palm. Circa 1640 A.D. This formerly belonged to Dr. Edward Jackson of Denver who received it from Dr. Casey Wood.
Dr. Edward Jackson's case of dissecting instruments.
Dr. Edward Jackson's leather pocket case of instruments.
Liebreich's Ophthalmoscope taken from the pocket of a dead German medical officer on the battlefield of France in World War I. This was presented to Dr. Chance by H. L. Harley, M. D. of Atlantic City for the Section on Ophthalmology.
Modification of Jaeger's Ophthalmoscope formerly belonging to Dr. William Hewson.
Jaeger's Ophthalmoscope which was used by Dr. Addinell Hewson.
Beale's Ophthalmoscope.

Presented by *Col. William Innes Forbes*, son of Dr. William Smith Forbes:
Framed lithograph of the "Barrack" Hospital at Scutari, Turkey, during the Crimean War.

Presented by *Dr. H. Pearce Lakin* of North Wales, Pa.:
Trial case of lenses used in teaching skioscopy in the old Polyclinic Hospital, by Dr. Edward Jackson.

Presented by *Dr. G. N. J. Sommer* of Trenton, N. J., the following medals:
Louis Pasteur.
Small "Century of Progress" Exposition medal—Chicago 1933.
Large "Century of Progress" Exposition medal—Chicago 1933.
Prof. F. Widal.
Dr. Theodor Billroth (2 schilling piece).

Presented by *Dr. Edward F. Corson:*
British War Medals as follows:
For Distinguished Conduct in the Field, World War I.
Ashanti Campaign 1900.
For Bravery in the Field.
Abyssinia, issued to members of Expeditionary Forces sent into Ethiopia in 1867.

Presented by *Gen. I. S. Ravdin*, Prof. of Research Surgery, University of Pennsylvania, commanding the 20th General Hospital, Assam:
Collection of Japanese medical supplies captured in the Burma Campaign.

Presented by the *Estate of Dr. Paul Sartain*, through Dr. Burton Chance:
Landolt's Ophthalmoscope in use about 1880.
Schiötz Tonometer.
Bailliart's Tonometer.
Set of instruments for ink staining corneal scars.
Mounted prisms for measuring the strength of eye muscles.
Chibrets's Chromoptometer.
Perrin's artificial eye with 12 painted models of backgrounds of the eye to exhibit affections.
Box of ivory handled eye instruments.
Geneva Lense Measure.

Retinoscope.

Heurteloup's artificial leech.

Presented by the *Estate of Dr. Paul Sartain:*

Zentmayer microscope and accessories.

Presented by *Mr. John Thompson Emlen,* through Dr. William N. Bradley:

Oil portrait of Samuel Emlen (1789–1828) by Sully. Dr. Samuel Emlen was Secretary of the College of Physicians from 1820 to 1828. This portrait was presented to the College and its acceptance recommended to Council by the Committee on College Collections with the understanding that it be given to the College as a permanent gift. Mr. John T. Emlen agreed to these conditions and the portrait becomes a part of the College Collections.

*Activities.* Permission was granted for the photographs of the oil portraits of Dr. Thomas S. Kirkbride and Dr. Astley P. C. Ashhurst, to be taken.

Oil portraits and photographs have been cleaned and new backs put on the photographs, when needed.

A paper entitled "Let Us Look Over the Collections of the College of Physicians" by Mrs. Ella N. Wade, curator, appeared in the *Transactions & Studies* of the College in June 1945.

Dr. Joseph McFarland was reappointed Honorary Custodian of College Collections for the year 1944-45, and Mrs. Ella N. Wade Custodian and Clerk-technician.

Oscar V. Batson
*Chairman*

# Annual Report of the Committee on Public Health, Preventive Medicine and Public Relations

In accordance with established precedent this Committee met with the Committee on Public Health and Preventive Medicine of the Philadelphia County Medical Society in joint meetings throughout the year. Fewer meetings were held than in previous years, due to the members' increased obligations relating to the war.

The following subjects were considered:

I. A major subject, considered at several meetings, was concerned with the position of Director of Public Health in Philadelphia. No personalities were considered. It was agreed all efforts should be directed towards impressing those in political control of appointments to the city government that in accordance with the appointment of health officers in other comparable cities, the Director of Public Health in Philadelphia should be a physician of both training and experience with tenure of office.

It was also agreed that the requirement of proper training should preferably include training in a recognized graduate school of public health and that a Director of Health should have had previous experience in public health work in a well recognized public or official position in a governmental unit. No Director of Public Health in Philadelphia has felt any security in office or has been able with any continuity to carry out far-sighted programs or reforms which require years of steady work and effort.

In view of the above considerations preliminary approaches of a political nature have been made by a small group consisting of the Co-Chairmen of the Joint Committee and the respective presidents of the Philadelphia County Medical Society and the Philadelphia College of Physicians. It has been proposed that such approaches and pressure be continued and increased in accordance with the wishes and under the direction of the Board of Directors of the Philadelphia County Medical Society and the Council of the Philadelphia College of Physicians, for the purpose of assisting the city government in moving towards the objectives mentioned.

II. At the request of a certain dairy, the subject of milk control was considered during the entire period of one meeting of the Joint Committee. The discussion revolved about the methods used in the Philadelphia area towards safeguarding the quality of milk. Extensive data were submitted for the Joint Committee's consideration. The members of the Joint Committee agreed that in case important public hearings were held concerning proper standards and safeguards relating to the quality of milk they would be glad to arrange a presentation of the position of the committee as related to these matters.

III. The subject of the needs of mental institutions, and in particular the Philadelphia State Hospital, occupied the entire period of a joint meeting of this committee, together with the Committee on Nervous and Mental Diseases of the Philadelphia County Medical Society.

The desperate situation of the State institutions was well outlined by Dr Charles A. Zeller, Superintendent, Philadelphia State Hospital. It was indicated by Dr Zeller that approximately 12 million dollars was being appropriated in the biennium 1945-47 by the state for mental institutions, whereas 98 million dollars was actually needed in order to bring them up to a satisfactory standard. The Joint Committee recommended that additional sums be appropriated to provide the necessary improvements and added facilities in the existing mental hospitals of the state.

IV. The deplorable conditions in commercial nursing homes were considered and the following action was taken:

Resolved, that the Committee ascertain from the Public Charities Association in what manner the Society can be of assistance in the solution of this problem.

*Further Resolved*, that the Committee recommend to the Board of Directors of the Philadelphia County Medical Society that proper legislation be

introduced into the State Legislature so as to give the Department of Welfare greater powers of enforcement.

V. Repeated discussions occurred concerning the quality of drinking water in Philadelphia and means of correction. Members of this committee have been assisting in a number of programs relating to the improvement of the water supply. It is agreed that all efforts must centre upon keeping this important subject continuously before the public for the purpose of obtaining legislative action in correcting what is probably one of the greatest of the City's public health hazards.

Joseph Stokes, Jr.
*Chairman*

# Annual Report of the Publication Committee

This report covers the four numbers of the *Transactions & Studies* published within the College's fiscal year ending November 30. 1945: namely, vol. 12, nos. 3 and 4, and vol. 13, nos. 1 and 2.

The total number of pages printed was 190, an increase of 26 pages over the total of last year's four issues.*

The editor has been disturbed at the late appearance of the issues. While he has himself been in some measure responsible for this, our printers freely lay claim to a like share in the responsibility. A very large part of their capacity has been devoted to work for the Government during the war, for which they have received proper governmental recognition; under the circumstances, there was no inclination on our part to press for personal advantages. Both houses aim now at returning as rapidly as possible to a more stable schedule.

All four of the endowed lectures arranged by the College were available foi publication, fortunately, and only one of the four arranged by the County Society was withheld from publication. In line with our desire to publish on occasion other lectures delivered at the College, though not necessarily directly under its auspices, we were gratified at being able to bring to our readers the thoughtful observations on cancer research in 1944 presented by Dr Shields Warren at a joint meeting of the College, the Philadelphia County Medical Society, and the Philadelphia Division of the American Cancer Society in April, 1945.

Readers of the *Studies* must lament with us that the death of Dr Joseph McFarland brings to an end the series of delightful articles which, under the general heading of "Rummaging in the Museum", he contributed to our pages in the past half-dozen years, the last of which appeared in our issue of last April. These articles, written with unusual literary skill and charm, did much to humanize the collections in the Mütter Museum and the College Collections, and unquestionably stimulated further donations to the collections. These departments of the College—and our readers—are fortunate that Dr McFarland's successor, Mrs Wade, had, even before his death, demonstrated in our pages that she is singularly well equipped to carry on his humanizing influence. While further articles from his pen will be greatly missed, others from hers may be pleasantly anticipated.

A summary of receipts and expenditures for the year follows:

*Receipts*

| | | |
|---|---|---|
| Appropriation | $633.76 | |
| Income from publication funds | 716.27 | |
| Sales and reprints | 62.88 | $1,412.91 |

*Expenditures*

| | | |
|---|---|---|
| Printing, mailing, and reprints | $1,383.64 | |
| Stenciling envelopes | 19.00 | |
| Miscellaneous | 10.27 | $1,412.91 |

W. B. McDaniel, 2d
*Editor*

Approved:
John Porter Scott
*Chairman*

* In last year's report the total number of pages for the year was incorrectly given as 162, instead of 164.

# Annual Reports of the Sections

## General Medicine

During the year there were the following changes in membership: deceased members: 2; members taken into the Armed Forces: 1; resignations: 1; total decrease in membership: 4. New members: 14. Total number of active members, December 7, 1945: 127.

Number of meetings held during the year 1945: 7. At 6 of these meetings the Section was addressed by out of town Speakers. Ten papers were given by members of the Section or their guests. The average attendance at each meeting was 115.

L. M. Tocantins
*Clerk*

## Medical History

No meeting of the Section has been held since 1941. It is anticipated that a re-organization meeting of the Section will be held in the spring of 1946, following the expected return of our chairman and a member of the Executive Committee from military service.

William G. Leaman, Jr.
*Clerk*

## Ophthalmology

The total membership of the Section is now 57. Of this number 51 have paid dues, six having been excused because of their membership in the Armed Forces of the United States.

The Eighth Annual de Schweinitz Lecture was delivered by Dr. Derrick Vail of Chicago, on November 15th.

The Zentmayer Prize was awarded to Dr. Irving H. Leopold for his paper on "Penicillin Therapy of Vitreous Infections."

George F. J. Kelly
*Clerk*

## Otolaryngology

During the last year there have been seven meetings, held in cooperation with the Philadelphia Laryngological Society. Like the previous year these meetings were arranged for alternatively by the two societies, and conducted respectively by the officers of those societies. The Section arranged for and conducted the December, February, April and October Meetings; the attendance was as follows:

| | Members | Guests | Total |
|---|---|---|---|
| December 1944 | 19 | 17 | 36 |
| February 1945 | 22 | 37 | 59 |
| April 1945 | 15 | 20 | 35 |
| October 1945 | 10 | 21 | 31 |

The total membership is 58.

The Section lost through death one member, Dr. Henry A. Miller. One new member was acquired, Dr. John V. Blady.

Oscar V. Batson
*Clerk*

## Section on Public Health, Preventive and Industrial Medicine

The Section has had three meetings during the year 1945, held on January the 22nd, April the tenth and November the 5th. The first meeting on January the 22nd was a joint meeting of the Section with the Section on General Medicine, and our Section was represented by Dr. Julia Morgan, who gave a paper on "Malaria—Today and Tomorrow." The second meeting was a symposium on Tuberculosis, with Dr. Gene Gillespie from the Department of Public Health of the United States, Dr. Katharine Boucot from the Philadelphia Tuberculosis and Health Association and Dr. Martin J. Sokoloff of the Department of Public Health giving papers. The last meeting was a symposium on Pneumonia and the papers were given by Mr. John B. McCann, Registrar, and Drs. Hobart A. Reimann and Harrison F. Flippin. The attendance at the Section Meetings has been only fair. There are 37 Fellows of the Section.

David A. Cooper
*Clerk*

# Transactions of the Sections

## SECTION ON GENERAL MEDICINE

*October 22, 1945*[1]

Evidence for Dietary Deficiency as the Etiology of Calcinosis and Scleroderma. John Lansbury, M.D. (Commentator: Allan D. Wallis, M.D.)

Intercapillary Glomerulosclerosis in Experimental Diabetes. F. D. W. Lukens, M.D., and F. C. Dohan, M.D.

Humoral Factors in Experimental Carcinogenesis. W. U. Gardner, PH.D.

*November 26, 1945*

Fat and Sugar Intolerance as a Cause of Gastrointestinal Symptoms. Louis Tuft, M.D., and Henry J. Tumen, M.D. (Commentator: T. Grier Miller, M.D.)

Further Studies on Therapy with Streptomycin. H. A. Reimann, M.D., A. H. Price, M.D., and W. F. Elias, M.D. (Commentators: Jonathan Rhoads, M.D., and Garfield G. Duncan, M.D.)

Endocrine Control of Lymphoid Tissue Structure and Function. Abraham White, PH.D.

*December 17, 1945*[2]

Russian Physiology and Physiologists. Detlev W. Bronk, PH.D.

Russian Science and Scientists. Jacob Heiman, M.D.

## SECTION ON OPHTHALMOLOGY[3]

*October 18, 1945*

Neurofibromatosis in Three Consecutive Generations: Case Presentation. Edith E. Harvey, M.D.

Surgical Treatment of Paralysis of the Superior Oblique Muscle. William E. Krewson, 3d, M.D.

Possible Ocular Pemphigus: Case Presentation. Joseph V. Klauder, M.D., and Alfred Cowan, M.D.

Herpes Zoster Ophthalmicus Appearing after Trauma. Joseph V. Klauder, M.D.

*November 15, 1945*

The Scleral Resection (Eyeball Shortening) Operation. Derrick T. Vail, M.D. (Eighth Annual de Schweinitz Lecture.)

*December 20, 1945*

Dietary Deficiency Causing Blindness. A. D. Beam, Cmdr, MC, USNR.

Closure of the Senile Cataract Incision by Burying a Corneoscleral Suture and the Entire Limbus Incision Line with a Sliding Conjunctival Flap from Above. P. H. Decker, M.D.

## SECTION ON OTOLARYNGOLOGY[4]

*October 24, 1945*[5]

The Rehabilitation of the Speech and Hearing Handicapped: a Panel Discussion by Members of the Staff of the Speech and Hearing Rehabilitation Unit, U. S. Naval Hospital, Philadelphia. Francis L. Lederer, Cmdr, MC, USNR; Priscilla Pittenger, Lt(jg), USNR; Harriet L. Haskins, Lt(jg), USNR; Eva A. Thompson, Lt(jg), USNR; D. E. Morley, Lt(jg), USNR; J. E. Taylor, Lt(jg), USNR; William G. Hardy, Lt(jg), USNR, *moderator*.

*November 21, 1945*[5]

A Study of Chronic Suppurative Otitis Media at the Pennsylvania School for the Deaf. William J. Hitschler, M.D., and Mary Frances

[1] Joint meeting with the Endocrine Society of Philadelphia.

[2] Joint meeting with the Philadelphia Chapter of the American-Soviet Medical Society.

[3] The transactions of this Section are customarily abstracted in the *American J. Ophthalmology* and the *Archives of Ophthalmology*.

[4] The transactions of this Section are customarily abstracted in the *Archives of Otolaryngology*.

[5] Joint meeting with the Philadelphia Laryngological Society.

Vastine, M.D. (Commentator: Thomas F. Furlong, Jr.)

Trans-maxillary Approach to the Para-nasal Sinuses. Ermiro de Lima, M.D. (Commentator: Romeo A. Luongo, M.D.)

Benign Tumor of the Esophagus: Case Presentation. Herman B. Cohen, M.D. (Commentator: Gabriel Tucker, M.D.)

## SECTION ON PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE

*November 5, 1945*

*Symposium on Pneumonia*

Incidence, Morbidity and Mortality of Pneumonia in Philadelphia for the Past Twenty Years. John B. McCann.

Diagnosis and Management of Non-bacterial Pneumonia. Hobart A. Reimann, M.D.

Diagnosis and Management of Bacterial Pneumonia. Harrison F. Flippin, M.D.

# List of the College Lectures, 1945*

*January 10*

THORN, GEORGE W. Asthenia of Adrenal and Thyroid Origin—Differential Diagnosis and Treatment[1].

*February 7*

KEEFER, CHESTER S. Penicillin (Nathan Lewis Hatfield Lecture XXIX). (*Transactions & Studies*, April, 1945.)

*March 14*

MEIGS, JOE VINCENT. The Early Diagnosis of Carcinoma of the Uterus. (*Transactions & Studies*, June, 1945.)

*April 4*

WOLFERTH, CHARLES C. Observations on the Diagnosis of Coronary Disease (Mary Scott Newbold Lecture LV). (*Transactions & Studies*, June, 1945.)

*September 19*

NEWITT, ARTHUR W. Post-War Objectives of Tuberculosis Control. (*Transactions & Studies*, December, 1945.)

*October 3*

WIENER, ALEXANDER S. Recent Advances in Knowledge of the Rh Blood Factors, with Special Reference to the Clinical Applications (Alvarenga Prize Lecture V). (*Transactions & Studies*, December, 1945.)

*November 14*

JONES, T. DUCKETT. The Medical Profession and the Present Rheumatic Fever Problem[1].

*December 5*

ALEXANDER, JOHN. The Widening Scope of Thoracic Surgery (Mary Scott Newbold Lecture LVI)[1].

* Held jointly with the Philadelphia County Medical Society. The February, April, October, and December lectures were arranged by and delivered at the College; the other lectures were arranged by the Society and delivered at its building.

[1] Not available for publication in full.

# Fellows

December 31, 1945

ELECTED

1912. Addison, William H. F., Medical Laboratories, Univ. of Pa.
1926. Adler, Francis Heed, 313 S. 17th St.
1914. Aiken, Thomas G., Berwyn, Pa.
1936. Aldridge, Fred Cutler, Wayne, Pa.
1936. Alexander, Fay Knight, Fitzgerald Mercy Hospital, Darby, Pa.
1906. Allen, Francis Olcott, Jr., 2216 Walnut St.
1932. Allen, Frederick H., 1711 Fitzwater St.
1935. Alpers, Bernard J., 111 North 49th St.
1905. Anspach, Brooke M., 1827 Spruce St.
1930. Appel, Kenneth E., 111 N. 49th St.
1905. Appleman, Leighton Francis, 308 S. 16th St.
1935. Armitage, George L., 400 E. 13th St., Chester, Pa.
1922. Arnett, John H., ~~1804 Pine~~ St. 2116 Pine St. Phila 3.
1942. *Aronson, Joseph D.
1941. *Aronson, Roland S.
1920. Astley, G. Mason, 812 N. 63rd St.
1944. Atkins, Joseph P., 1201 Knox Rd., Wynnewood, Pa.
1935. Atlee, John L., 37 E. Orange St., Lancaster, Pa.
1935. Atlee, John L., Jr., 37 E. Orange St., Lancaster, Pa.
1914. Austin, J. Harold, 821 Maloney Clinic, Univ. of Pa.
1935. Bach, Theodore F., 1900 Rittenhouse Sq.
1942. Bachman, Carl, Univ. of Pa. Hospital.
1937. Bacon, Emily P., 1930 Chestnut St.
1916. Balentine, Percy L., 407 Weightman Bldg., 1524 Chestnut St.
1898. Balliet, Tilghman M., 3920 Sansom St.
1940. Banes, Charles C. A., 2043 N. 12th St.
1934. Bank, Joseph, 2210 N. 9th Ave., Phoenix, Arizona.
1940. Barba, Philip S., 222 W. Harvey St., Germantown.
1943. Barden, Robert P., 3400 Spruce St.
1911. Barnard, Everett P., 1820 S. Rittenhouse Sq.
1939. Barnshaw, Harold D., 406 Cooper St., Camden, N. J.
1939. Bartle, Harvey Jr., 133 S. 36th St.
1924. Bartle, Henry J., 1930 Chestnut St.
1931. Bates, William, 2029 Pine St.
1932. Batson, Oscar V., 3502 Hamilton St.
1921. Bauer, Edward L., 1609 Spruce St.
1933. Bauer, John T., Pennsylvania Hospital.
1939. Baumann, Frieda, 1930 Chestnut St.
1922. Bazett, Henry C., Medical School, Univ. of Pa.
1908. Beardsley, E. J. G., 1919 Spruce St.
1930. Beardwood, Joseph T., Jr., 2031 Locust St.
1935. Beerman, Herman, 2422 Pine St.
1932. Behney, Charles A., 3722 Chestnut St.
1942. Behrend, Albert, 255 S. 17th St.

* On active service.



LIBRARY OF THE
COLLEGE OF PHYSICIANS
OF PHILADELPHIA

1945. Behrend, Bernard, 5910 Greene St.
1934. Behrend, Moses, 255 S. 17th St.
1930. Belk, William Parks, Times Medical Bldg., Ardmore, Pa.
1936. Bell, Benjamin Tertius, 1930 Chestnut St.
1943. *Berk, J. Edward. 255 So. 17 St.
1941. Bernstein, Mitchell, 1321 Spruce St.
1937. Bertolet, J. Allan, 1530 Locust St.
1934. Biddle, Sydney Geoffrey, 255 S. 17th St.
1918. Billings, Arthur E., 2020 Spruce St.
1917. Birdsall, Joseph C., 139 Booth Lane, Haverford, Pa.
1933. Bishop, Paul A., Pennsylvania Hospital.
1944. Blady, John V., 222 Meeting House La., Merion, Pa.
1917. Block, Frank B., 136 S. 16th St.
1929. Bockus, Henry L., 250 S. 18th St.
1928. Boles, Russell S., Rittenhouse Plaza.
1923. Bond, Earl D., 111 N. 49th St.
1911. Bonney, Charles W., 255 S. 17th St.
1924. Boon, David J., 3131 W. Penn St.
1931. Bortz, Edward Le Roy, 2021 W. Girard Ave.
1921. Borzell, Francis Frank, 4940 Penn St., Frankford.
1936. Bostwick, Delazon Swift, 106 Linwood Ave., Ardmore, Pa.
1928. Bothe, Albert E., 255 S. 17th St.
1928. Bothe, Frederick A., 255 S. 17 St.
1923. Bower, John O., 2008 Walnut St.
1942. Bowie, Morris A., 910 Old Lancaster Road, Bryn Mawr, Pa.
1907. Boyer, Henry P., 4602 Baltimore Ave.
1925. Boykin, Irvine M., 136 S. 16th St.
1929. Bradbury, Samuel, 151 W. Coulter St.
1907. Bradley, William Nathaniel, 1725 Pine St.
1942. Branen, William, Whitby & Cypress Ave., Yeadon, Pa.
1921. Bransfield, John W., 2101 Spruce St.
1917. Bromer, Ralph S., 318 Milbank Road, Bryn Mawr, Pa.
1936. Brown, Charles L., 1030 Indian Creek Rd.
1936. Brown, Clark E., Lankenau Hospital.
1932. Brown, Claude P., 1930 Chestnut St.
1919. *Brown, Henry P., Jr.
1939. Brust, Raymond W., 4710 Chester Ave.
1930. Bucher, Carl Joseph, The Westbury, 15th & Spruce Sts.
1943. Buerki, Robin C., University of Pa.
1928. Burden, Verne G., 255 S. 17th St.
1940. Burnett, W. Emory, 3401 N. Broad St.
1941. Butler, Miriam, 1831 Chestnut St.
1906. Butler, Ralph, 1930 Chestnut St.
1907. Cadwalader, Williams B., 133 S. 36th St.
1928. Campbell, Edward H., Spruce Street Medical Bldg., 19th & Spruce Sts.
1944. Campion, Richard J., Penllyn Rd., Springhouse, Ambler, Pa.
1931. Cantarow, Abraham, 1025 Walnut St.
1935. Carey, Lawrence S., 1930 Chestnut St.
1931. Cariss, Walter L., 2043 Walnut St.
1930. Carpenter, Chapin, 1930 Chestnut St.
1905. Carpenter, Herbert B., 1805 Spruce St.

* On active service.

1926. Carpenter, Howard Childs, 1805 Spruce St.
1895. Carpenter, John T., 1930 Chestnut St.
1917. Carson, John B., 1802 Pine St.
1922. Case, Eugene A., 63 W. La Crosse Ave., Landsdowne, Pa.
1937. Castallo, Mario A., 1621 Spruce St.
1943. Castigliano, S. Gordon, 1012 Hampstead Rd., Penfield Downs, Del. Co., Pa.
1933. Chamberlain, W. Edward, Temple University Hospital.
1939. Chamberlain, George W., Reading Hospital, Reading, Pa.
1900. Chance, Burton, 317 S. 15th St.
1945. Chance, Burton, Jr., 1726 Spruce St.
1939. Charr, Robert Kyun Hyun, 2038 Locust St.
1941. *Cheleden, John.
1945. Cianfrani, Theodore, 1930 Chestnut St.
1939. Ciccone, Emmet F., 2021 Murray St.
1929. Clark, Eliot R., 315 S. 41st St.
1934. Clark, Jefferson Hamer, 3701 N. Broad St.
1926. Clerf, Louis H., 1530 Locust St.
1910. Cloud, J. Howard, 11 W. Montgomery Ave., Ardmore, Pa.
1903. Coates, George Morrison, 1721 Pine St.
1908. Codman, Charles A. E., S.E. Corner 42d and Spruce Sts.
1941. Cohen, J. Gershon, 255 S. 17th St.
1907. Cohen, Myer Solis-, 2110 Spruce St.
1888. Cohen, S. Solis-, Mountain & Cheltenham Aves.
1920. Cole, Charles J., 7926 Park Ave., Elkins Park, Pa.
1934. Colgan, Robert C., 5882 No. Marshall St.
1934. Collins, Leon Howard, Jr., 133 S. 36th St.
1943. Colonna, Paul C., Univ. of Pa. Hospital.
1945. Coonel, Pauline, 5908 Greene St.
1930. Cooper, David A., 1520 Spruce St.
1941. *Cornelius, Chalmers E.
1911. Cornell, Walter S., Board of Public Education, Parkway and 21st St.
1945. Corrigan, Patrick H., 1720 S. Broad St., Trenton, N. J.
1914. Corson, Edward F., 136 S. 16th St.
1930. *Cottrell, James E.
1924. Cowan, Alfred, 1930 Chestnut St.
1940. Cowan, Thomas H., 1930 Chestnut St.
1904. Craig, Frank A., The Henry Phipps Institute, 7th and Lombard Sts.
1942. Craighill, Margaret D., Woman's Medical College of Pa.
1907. Crampton, George S., 2031 Locust St.
1937. *Crane, Martin P., U. S. Naval Hosp.
1920. Creighton, William J., 37 S. 20th St.
1941. Creskoff, Adolph J., 3400 Spruce St.
1920. Cross, George H., Chester, Pa.
1917. Cross, Sumner H., P. O. Box 126, Jenkintown, Pa.
1921. Crossan, Edward T., 5324 Wayne Ave.
1940. Crowe, Aldrich C., 735 Atlantic Ave., Ocean City, N. J.
1904. Cruice, John M., 407 S. 22d St.
1937. Crump, Jean, 1930 Chestnut St.
1937. Curtis, Lawrence, 255 S. 17th St.
1934. *Custer, R. Philip.
1941. *Cuttle, Tracy D.

* On active service.

1938. Dannenberg, Arthur M., 235 S. 15th St.
1919. Davies, John R., Jr., 2 E. Chestnut Ave., Chestnut Hill.
1936. Davis, David M., 255 S. 17th St.
1937. *Davis, Perk Lee.
1916. Davis, Warren Beagle, 135 S. 18th St.
1935. Deaver, J. Montgomery, 1830 Delancey Pl.
1902. Dehoney, Howard, 240 S. 13th St.
1935. Deibert, Irvin Elmer, 538 Cooper St., Camden, N. J.
1924. Deichler, L. Waller, 1930 Chestnut St.
1923. De Long, Perce, 37 S. 20th St.
1928. Dewees, A. Lovett, Times Medical Bldg., Ardmore, Pa.
1924. Dillon, Edward S., 2016 DeLancey St.
1932. Dintenfass, Henry, 1305 Spruce St.
1920. Diven, John, 1827 Delancey St.
1941. Dixon, Harold M., 4107 Chester Ave.
1920. Doane, Joseph C., 19th and Spruce Sts.
1942. Donnelly, Edward J., 1321 Spruce St.
1933. Donnelly, Joseph C., 255 S. 17th St.
1937. Donnelly, Robert T. M., 255 S. 17th St.
1907. Dorrance, George M., 2101 Spruce St.
1933. Downs, T. McKean, 921 Mt. Pleasant Rd., Bryn Mawr, Pa.
1945. Dozzi, Daniel Louis, 27 E. Willow Grove Ave.
1910. Drayton, William, Jr., 2028 Delancey St.
1935. *Duane, William, Jr.
1944. Dublin, George J., 1930 Chestnut St.
1944. Dugger, John H., 3902 Vaux St.
1935. Duncan, Garfield G., 330 S. 9th St.
1937. Dunn, Charles W., 269 S. 19th St.
1942. Durant, Thomas M., 3401 N. Broad St.
1942. Dyer, W. Wallace, 2016 Delancey St.
1935. Eads, John T., 2029 Delancey St.
1911. Earnshaw, Henry C. Bryn Mawr, Pa.
1936. Easby, Mary Hoskins, 1930 Chestnut St.
1937. Edeiken, Joseph, 1832 Spruce St.
1944. Eger, Sherman A., 2029 Delancey St.
1944. Ehrich, William E., 236 W. Hortter St.
1930. Eiman, John, Cynwyd, Pa.
1911. Eliason, Eldridge L., 326 S. 19th St.
1939. Ellis, Van Mashburn, 1530 Locust St.
1928. Ellison Richard T., 269 S. 19th St.
1936. Ellson, J. Vernon, Glendale Rd. & Chestnut St., Upper Darby, Pa.
1904. Elmer, Walter G., 1801 Pine St.
1945. English, O. Spurgeon, 255 S. 17th St.
1937. Elsom, Kendall A., 133 S. 36th St.
1934. Ely, William C., 3912 Chestnut St.
1932. Engel, Gilson G., 255 S. 17th St.
1942. Erb, William H., 4 Morton Ave., Ridley Park, Pa.
1893. Eshner, Augustus A., 1019 Spruce St.
1944. Estes, William L., Jr., Bethlehem, Pa.
1905. Evans, William, 500 W. Gay St., West Chester, Pa.

* On active service.

1922. Farley, David L., 4429 Larchwood Ave.
1903. Farr, Clifford B., Bryn Mawr, Pa.
1945. Farrar, George Elbert, Jr., 425 Tregaron Rd., Bala-Cynwyd, Pa.
1930. Farrell, John T. Jr., 255 S. 17th St.
1935. Ferguson, Lewis Kraeer, 133 S. 36th St.
1936. Fetter, Ferdinand, 322 S. 21st St.
1945. Fetter, John S., 2208 Murray St.
1935. Fetter, Theodore R., 255 S. 17th St.
1924. Fewell, Alexander G., 1924 Pine St.
1943. Finkelstein, Arthur, 645 Overhill Rd., Ardmore, Pa.
1945. Fiske, Frederick A., 1530 Locust St.
1928. Fitz-Hugh, Thomas, Jr., 2016 Delancey Pl.
1928. Flick, John B., Mormont Plaza, Bryn Mawr, Pa.
1939. Flippin, Harrison F., 255 S. 17th St.
1940. Forrester, James S., Univ. of Pa. Hospital.
1941. Fox, C. Calvin, 1806 Spruce St.
1906. Fraley, Frederick, 71st and City Line, Overbrook, Pa.
1941. *Frazier, William Doane.
1939. Freeman, Norman E., Dept. of Research Surgery, Univ. of Pa.
1935. Fridy, Cyrus Ward, 506 Kenwood Rd., Drexel Park, Pa.
1942. Friedman, Reuben, 877 N. 6th St.
1933. Fritch, James Scott, 269 S. 19th St.
1937. Fritz, Herbert H., Pennswood Rd., Bryn Mawr, Pa.
1940. *Fry, Kenneth E.
1935. Fry, Wilfred Eyles, 1819 Chestnut St.
1937. Furlong, Thomas F., Jr., Times Medical Building, Armore, Pa.
1935. Gammon, Geo. D., Univ. of Pa. Hospital.
1931. Garner, Vaughn C., Germantown Professional Building.
1935. *Geist, Donald C.
1917. Gerhard, Arthur H., 1615 N. Delaware Ave.
1899. Gibbon, John H., Media, Pa.
1934. Gibbon, John H., Jr., 4035 Pine St.
1939. Gibson, Glen Gregory, 255 S. 17th St.
1944. Gifford, Edward S., Jr., 1913 Spruce St.
1933. Gifford, U. Grant, Kennett Square, Pa.
1920. Gill, A. Bruce, 1930 Chestnut St.
1931. Gilman, Robert Louis, Wallingford, Pa.
1927. Gilmour, William R., 413–14 Weightman Bldg., 1524 Chestnut St.
1931. Giordano, Anthony A. S., 1819 S. Broad St.
1906. Gittings, John C., Harwood, Md.
1906. Goepp, R. Max, 1333 Chestnut St.
1945. Goldberg, Samuel J., 1723 Pine St.
1933. Goldburgh, Harold L., 1932 Spruce St.
1935. Goldsmith, N. Ralph, 136 S. 16th St.
1905. Gordon, Alfred, 1520 Spruce St.
1928. Gordon, Burgess L., 1832 Spruce St.
1937. Gordon, William, 1721 Pine St.
1941. Gouterman, Joseph I., 334 W. School Lane.
1894. Graham, Edwin E., 1713 Spruce St.
1926. Grant, Francis Clark, Univ. of Pa. Hospital.

* On active service.

1933. Greenbaum, Sigmund S., 320 S. 18th St.
1940. Greene, Lloyd B., 136 S. 16 St.
1932. *Griffith, George C.
1934. Griffith, John Q., Jr., 214 Glencoe Ave., Upper Darby, Pa.
1945. Griffiths, John E., Mermont Apartments, Bryn Mawr, Pa.
1941. *Groff, Robert A.
1933. Gruber, Charles M., 128 Overhill Rd., Cynwyd, Pa.
1932. Guequierre, Jacques P., Mermont Plaza, Bryn Mawr, Pa.
1944. Gunter, John H., 1306 Knox Rd., Wynnewood, Pa.
1945. György, Paul, Department of Pediatrics, Univ. of Pa.
1935. Hadden, Samuel B., 37 S. 20th St.
1945. Hahn, George A., 255 S. 17th St.
1935. Haines, Harlan F., 134 S. State Rd., Upper Darby, Pa.
1939. Hamblock, Leonard C., 255 So. 17th St.
1894. Hamill, S. McC., 1822 Spruce St.
1897. Hand, Alfred, 1724 Pine St.
1938. *Hand, John G.
1932. Harris, Stanley E., Lansdowne, Pa.
1929. Harrison, Francis G., 1900 Spruce St.
1933. Harrison, William John, 135 S. 17th St.
1903. Hart, Charles D., 420 W. Mermaid Lane, Chestnut Hill.
1941. Hartley, Harriet L., 1719 Rittenhouse Square.
1932. Hartman, J. Calvin, 50 W. Walnut Lane.
1926. Hartmann, Fred L., 1914 Pine St.
1935. Haskell, Benjamin F., 1426 Spruce St.
1907. Hatfield, Charles James, Henry Phipps Institute, 7th and Lombard Sts.
1911. Heed, Charles R., 1205 Spruce St.
1944. Herbut, Peter A., Jefferson Medical College Hospital.
1927. Herman, Leon, 136 S. 16 St.
1944. Hershey, J. Ivan, 152 Pennsylvania Ave., Bryn Mawr, Pa.
1924. Hewson, William, 2031 Locust St.
1924. Hirst, John C., 2d, 500 N. 20th St.
1944. Hirst, Otto C., 255 S. 17th St.
1908. Hitchens, Arthur Parker, Medical School, Univ. of Pa.
1943. Hitschler, William J., 8840 Germantown Ave.
1944. Hneleski, Ignatius S., Phila. General Hosp.
1943. Hockaday, Agnes, 316 Shadeland Ave., Drexel Hill, Pa.
1939. Hodes, Philip J., Univ. of Pa. Hospital.
1931. Holland, H. Albert, 8200 Crittenden St., Chestnut Hill.
1933. Hollingshead, Irving W., 123 S. 18th St.
1932. Hollingsworth, I. Pemberton P., 411 N. Walnut St., West Chester, Pa.
1919. Hopkins, Arthur H., 1726 Pine St.
1925. Hopkinson, R. Dale, Jenkintown, Pa.
1944. Housel, Edmund L., 255 S. 17th St.
1928. Houser, Karl Musser, 2010 Spruce St.
1938. Howell, John Carnett, 326 S. 19th St.
1937. Hughes, Joseph, 418 Mulberry Lane, Haverford, Pa.
1939. Hughes, P. Boland, 419 Hillbrook Rd., Bryn Mawr, Pa.
1923. Hume, John E., 37 S. 20th St.
1921. Hunter, Robert John, 928 N. 63rd St.

* On active service.

1926. Husik, David N., 1820 Spruce St.
1934. Hustead, Frank H., 5112 N. Broad St.
1935. Ingleby, Helen, Jewish Hospital, York & Tabor Rds.
1921. Ivy, Robert H., 1930 Chestnut St.
1917. Jackson, Chevalier, 255 S. 17th St.
1932. Jackson, Chevalier L., 255 S. 17th St.
1934. Jacobs, Maurice S., 1831 De Lancey Place.
1941. *Jeffers, William A.
1928. John, Rutherford L., 256 S. 21st St.
1942. *Johnson, Julian.
1938. *Johnson, Thomas A.
1918. Jonas, Leon, 255 S. 17th St.
1943. *Jones, Charles Alexander.
1924. Jones, Harold W., 1930 Chestnut St.
1900 Judson, Charles F., 252 Kent Road, Wynnewood, Pa.
1902. Jump, Henry Draper, 1530 Locust St.
1936. Kain, Thomas M., 403 Cooper St., Camden, N. J.
1938. Kasper, Kelvin A., 135 S. 18th St.
1945. Katz, G. Henry, 111 N. 49th St.
1941. Kauffman, M. Luther, Medical Arts Bldg., Jenkintown, Pa.
1938. Keeler, Harold R., 136 S. 16th St.
1935. Kelley, George F. J., N.E. Cor. 20th and Chestnut Sts.
1932. Kelly, Herbert T., 1900 Spruce St.
1912. Kelly, Thomas C., 105 School Lane.
1941. Kennedy, Patrick J., 6910 Market St., Upper Darby, Pa.
1921. *Kern, Richard A.
1935. Keyes, Baldwin L., 2031 Locust St.
1930. Kimbrough, Robert A., Jr., 807 Spruce St.
1936. *King, Orville C.
1920. Klauder, Joseph V., 1934 Spruce St.
1920. Klein, Thomas, 250 S. 18th St.
1934. Kline, Oram R., 414 Cooper St., Camden, N. J.
1932. Klopp, John W., 600 W. Olney Ave.
1943. Kneedler, William H., 8801 Crefeld St.
1919. Knipe, Norman L., 1930 Chestnut St.
1908. Knowles, Frank C., 2035 Spruce St.
1938. Knox, Andrew, 1930 Chestnut St.
1925. Knox, Harry E., 719 66th Ave., Oak Lane.
1945. Kobler, H. B., 858 N. 63rd St.
1914. Kolmer, John A., Cynwyd, Pa.
1936. Konzelmann, Frank Williamson, 304 Shore Rd., Absecon, N. J.
1941. *Krall, J. Thomas.
1941. Krewson, William E., 3rd, 1930 Chestnut St.
1914. Krumbhaar, Edward B., School of Medicine, Univ. of Pa.
1944. LaMotte, William O., Medical Arts Bldg., Wilmington, Del.
1907. Langdon, H. Maxwell, 1530 Locust St.
1933. Langdon, Roy L., 5917 Greene St., Germantown.
1941. *Langner, Paul H., Jr.
1945. Lansbury, John, 3401 N. Broad St.
1934. Laplace, Louis B., 200 Glenn Rd., Ardmore, Pa.

* On active service.

1926. Laws, George M., 1907 Spruce St.
1936. Leaman, William G., Jr., 3700 Baring St.
1920. Leavitt, Frederic Headley, 1527 Pine St.
1941. Leberman, Paul R., 136 S. 16th St.
1934. Lee, Thomas B., 622 Cooper St., Camden, N. J.
1908. Lee, Walter Estell, 1833 Pine St.
1942. Lehman, James A., 1815 Spruce St.
1936. Lehrfeld, Louis, 1321 Spruce St.
1944. Lell, William A., 203 W. Chestnut Ave., Chestnut Hill.
1935 Lemmon, William T., 1930 Chestnut St.
1943. Leopold, Irving H., Univ. of Pa. Hospital.
1920. Leopold, Simon S., 2025 Spruce St.
1944. Lettiere, Anthony J., 425 E. State St., Trenton, N. J.
1933. Levering, J. Walter, Abington Memorial Hospital, Abington, Pa.
1915. Lewis, Fielding O., Providence Road, Media, Pa.
1938. *Lewis, James P.
1936. Lillie, Walter I., 255 S. 17th St.
1940. Limberger, William A., 301 S. Church St., West Chester, Pa.
1938. Lindauer, M. August, 133 S. 36th St.
1927. Lindsey, Walter H., 810 W. Dauphin St.
1936. Lintgen, Charles, 1930 Chestnut St.
1945. Lisker, Samuel, 1930 Chestnut St.
1944. Livezey, Mary M., 7200 Cresheim Rd.
1936. Llewellyn, Thomas H., 910 N. 63rd St.
1907. Lodholz, Edward, Medical Laboratories, Univ. of Pa.
1931. Loewenberg, Samuel A., 1905 Spruce St.
1938. Long, Charles-Francis, 1836 Delancey St.
1933. *Long, Esmond R.
1935. Long, William L., 2025 Walnut St.
1893. Longaker, Daniel, 5702 Overbrook Ave.
1931. Longaker, Edwin P., 41 E. Montgomery Ave., Ardmore, Pa.
1944. Loudenslager, Paul E., 2101 Spruce St.
1942. Lownes, John B., 136 S. 16th St.
1936. Lucchesi, Pascal Francis, Phila. Hospital for Contagious Diseases.
1921. *Lucké, Balduin H. E.
1932. Lukens, Francis D. W., Univ. of Pa. Hospital.
1938. Lukens, Philip Jefferson, 158 E. Butler Ave., Ambler, Pa.
1930. Lukens, Robert M., Medical Arts Bldg., 16th and Walnut Sts.
1929. Lull, Clifford, B., Women's Bldg., Penna. Hosp., 807 Spruce St.
1939. Luongo, Romeo A., 2054 Locust St.
1919. Lynch, Frank B., Jr., Germantown Hosp., Penn and Chew Sts.
1914. Lyon, B. B. Vincent, Box 955, Winter Park, Fla.
1933. McAndrews, Leo F., Mermont Plaza, Bryn Mawr, Pa.
1932. McCahey, James F., 1534 Pine St.
1900. McCarthy, Daniel J., 2025 Walnut St.
1936. McCarthy, Patrick A., Central Medical Bldg.
1935. *McClenahan, William U.
1931. McCloskey, Edward, 7 E. Chestnut Ave., Chestnut Hill.
1942. McCloskey, John F., 8720 Germantown Ave.
1935. McConnell, James W., 20th and Chestnut Sts.

* On active service.

1934. McCouch, Grayson P., Medical School, Univ. of Pa.
1938. McCrea, Lowrain E., 1930 Chestnut St.
1937. McCutcheon, Morton, Alden Park Manor, Germantown.
1942. McDonald, P. Robb, 255 S. 17th St.
1945. McGee, Lemuel Clyde, Hercules Powder Company, Wilmington, Del.
1937. *McGuinness, Aims C.
1940. *McLaughlin, Edward F.
1933. *McLaughlin, James S.
1924. McMillan, Thomas M., 2044 Locust St.
1924. McPhedran, F. Maurice, Germantown Hosp., Penn and Chew Sts.
1943. Macfarlan, Douglas, 1805 Chestnut St.
1932. Macfarlane, Catharine, 136 S. 16 St.
1936. MacMurtrie, Wm. J., 912 S. 49th St.
1939. Macneill, Norman N., 5807 Chew St.
1935. Maeder, LeRoy M. A., 206 S. 13th St.
1935. Maier, Ernest G., 1323 N. 15th St.
1914. Maier, F. Hurst, Wood-Norton Apts., Johnson and Wayne, Germantown.
1942. Manges, Lewis C., Jr., 319 S. 16th St.
1936. Mann, Bernard, 2019 Pine St.
1937. Margolies, Alexander, 1836 Delancey St.
1941. Martin, James R., 136 S. 16 St.
1935. *Mason, James B.
1935 Matthews, Robert A., 111 N. 49th St.
1939. May, Hans, 255 S. 17th St.
1932. *Meade, Richard H., Jr.
1934. *Mecray, Paul M.
1914. Mencke, J. Bernhard, 1816 Spruce St.
1941. *Mendell, Theodore H.
1943. Meranze, David R., 1031 Lakeside Ave.
1937. Meyer, George Phillip, 410 Haddon Ave., Camden, N. J.
1935. Miller, Ford A., 4016 Chestnut St.
1934. Miller, Hugh McCauley, 1614 Locust St.
1939. Miller, Malcolm W., 255 S. 17th St.
1939. Miller, Merle M., 6013 Greene St.
1932. Miller, M. Valentine, 114 W. Phil-Ellena St.
1921. Miller, T. Grier, Univ. of Pa. Hospital.
1937. Missett, Joseph Vincent, Jr., 1814 Spruce St.
1904. Mitchell, Charles Franklin, 2003 Pine St.
1932. Mohler, Roy W., 1806 Spruce St.
1936. *Montgomery, Hugh.
1936. Montgomery, John B., 1930 Chestnut St.
1932. Montgomery, Thaddeus L., 2031 Locust St.
1928. Moon, Virgil H., Jefferson Medical College.
1935. Moore, John Royal, Beury Bldg., Broad St. and Erie Ave.
1924. Moorhead, Stirling W., 1523 Pine St.
1936. *Morgan, David R.
1893. Morris, Elliston J., 439 Midland Ave., St. Davids, Del. Co., Pa.
1944. Morris, Harold H., Villa Nova, Pa.
1945. Morris, I. Paul, 255 S. 17th St.
1941. Mucklé, Craig Wright, Haverford, Pa.

* On active service.

1929. Mudd, Stuart, Department of Bacteriology, Medical School, Univ. of Pa.
1935. Mullen, Carroll Richard, 2025 Locust St.
1934. *Mullen, Edward A.
1905. Muller, George P., 326 S. 19th St.
1930. Murphy, Douglas P., University Hospital.
1934. Murphy, Eugene C., 1841 S. Broad St.
1905. Mutschler, Louis H., 1625 Spruce St.
1945. Naide, Meyer, 2034 Spruce St.
1936. Nelson, Guy M., 255 S. 17th St.
1943. Nelson, Waldo E., 615 Moreno Rd., Narberth, Pa.
1905. Newcomet, William S., 3501 Baring St.
1938. Newton, Zachariah B., 601 E. Sedgwick St.
1935. Nicholson, Jesse Thompson, 1726 Spruce St.
1899. Nicholson, William Rufus, 1930 Chestnut St.
1941. Nisbet, Verner, 254 S. 45th St.
1905. Norris, Charles C., Darby and Goshen Roads, Bryn Mawr, Pa.
1938. *Norris, Robert F.
1941. *North, John Paul.
1941. Odenatt, Wm. Burrill, 1213 W. Lehigh Ave.
1913. O'Neal, Alexander Hay, St. Davids, Pa.
1936. *Orr, Theodore E.
1913. Outerbridge, George W., 1927 Spruce St.
1915. Owen, Hubley R., 319 S. 16th St.
1897. Packard, Francis R., 304 S. 19th St.
1909. Parish, Benjamin Dores, 1927 Spruce St.
1945. *Park, Felix Roman.
1940. Parker, Alan P., Radnor & Fisher's Rds., Bryn Mawr, Pa.
1944. Paschkis, Karl E., Jefferson Medical College.
1931. Paul, John Davis, 3112 N. Broad St.
1932. Payne, Franklin L., Univ. of Pa. Hospital.
1943. Pearson, Gerald H., 111 N. 49th St.
1922. Pelouze, P. S., 1216 Drexel Ave., Drexel Hill, Pa.
1909. Pemberton, Ralph, Paoli, Pa.
1930. Pendergrass, Eugene P., Univ. of Pa. Hospital.
1932. Pennell, Howard Y., West Chester, Pa.
1944. *Pennypacker, Charles S.
1939. *Pepper, D. Sergeant.
1914. Pepper, O. H. Perry, Univ. of Pa. Hospital.
1902. Pepper, William, School of Medicine, Univ. of Pa.
1916. Percival, Milton Fraser, 2332 S. Broad St.
1942. Perkins, William Harvey, 1025 Walnut St.
1940. Pessel, Johannes F., 224 West State St., Trenton, N. J.
1937. Pettit, Horace, P.O. Box 96, Gladwyne, Pa.
1905. Pfahler, George E., 1930 Chestnut St.
1915. Pfeiffer, Damon B., Meadowbrook, Pa.
1935. Phillips, Arthur W., 3904 Walnut St.
1911. Piersol, George Morris, Univ. of Pa. Hospital.
1933. *Pillsbury, Donald M.
1922. Pleasants, Henry, Jr., West Chester, Pa.
1937. Polk, David Stewart, Rosemont, Pa.

* On active service.

1932. Porter, Roland De Lance, Jenkintown, Pa.
1931. Pryor, Charles Allen, 255 S. 17th St.
1943. *Radbill, Samuel X.
1945. Rakoff, Abraham Edward, 2001 Delancey St.
1931. Ramsey, Frank M., Chestnut Hill.
1913. Randall, Alexander, 136 S. 16 Street.
1941. Rankin, Charles A., Ludlow & Heather Rd., Upper Darby, Pa.
1926. Ravdin, I. S., Univ. of Pa. Hospital.
1941. Rea, Marion Hague, 141 Montgomery Ave., Bala-Cynwyd, Pa.
1938. *Read, Hilton Shreve.
1928. Reese, Warren S., 1901 Walnut St.
1925. Reeves, Rufus S., 2227 Spruce St.
1931. Regester, Robert P., 255 S. 17th St.
1920. Rehfuss, Martin E., 131 St. George's Rd., Ardmore, Pa.
1921. Reiff, E. Paul, 1927 Spruce St.
1937. Reimann, Hobert A., Jefferson Hospital.
1919. Reimann, Stanley P., 703 W. Phil-Ellena St.
1923. Repplier, Sidney J., 373 Roumfort Rd., Mt. Airy.
1945. Rhoads, Jonathan E., University Hospital.
1936. Richards, James L., Haverford Villa, Ardmore, Pa.
1919. Richardson, Russell, 320 S. 16th St.
1919. Ridpath, Robert F., 1737 Chestnut St.
1942. Riggs, Helena E., 37 S. 20th St.
1936. Ritter, Joseph A., 2405 N. 54th St.
1933. de Rivas, Damaso, 1831 Chestnut St.
1942. Rivers, Thurston D., 111 N. 49th St.
1932. *Robbins, Frederick R.
1939. Roberts, Ella, 133 S. 36th St.
1944. Roberts, Joseph E., 403 Cooper St., Camden, N. J.
1899. Roberts, Walter, 1921 Spruce St.
1932. Robertson, Harold F., 327 S. 17th St.
1903. Robertson, William Egbert, 327 S. 17th St.
1938. Roche, Philip Q., 255 S. 17th St.
1912. Rodman, John Stewart, 1726 Spruce St.
1934. Rogers, Harry L., Riverton, N. J.
1928. Rose, Edward, 426 Owen Rd., Wynnewood, Pa.
1936. Rose, Elizabeth Kirk, 426 Owen Rd., Wynnewood, Pa.
1932. Rothrock, Harry A., West Chester, Pa.
1936. Rothschild, Norman, 245 S. 16th St.
1933. Rowntree, Leonard George, 1520 Spruce St.
1937. Roxby, John B., R.D. 1, Souderton, Pa.
1941. *Royster, Hubert A., Jr.
1943. Rubin, Mitchell I., 1740 Bainbridge St.
1933. Rudolphy, Jay Besson, 230 S. 21st St.
1945. Rynes, Samuel E., 334 S. 21st St.
1944. Sampson, David Alan, 726 Braeburn Lane, Penn Valley, Narbeth, Pa.
1936. Sands, Joseph Evans, Rosemont, Pa.
1908. Sautter, Albert C., Germantown Professional Bldg.
1920. Scarlett, Hunter W., 230 S. 21st St.
1939. Scattergood, Joseph, Jr., 115 S. High St., West Chester, Pa.

* On active service.

1917. Schaeffer, J. Parsons, 4634 Spruce St.
1929. Scheffey, Lewis C., 255 S. 17th St.
1942. *Scheie, Harold G.
1945. Schell, James F., 2506 S. 20th St.
1929. Schenck, Harry P., 1235 Wyngate Rd., Wynnewood, Pa.
1945. Schlezinger, Nathan S., Medical Tower Building.
1917. Schnabel, Truman G., 1704 Pine St.
1917. Schoff, Charles H. Media, Pa.
1928. Schofield, Frederick S., 425 W. Chelten Ave.
1921. Schumann, Edward A., 1814 Spruce St.
1930. Scott, John Porter, 1740 Bainbridge St.
1940. *Scott, T. F. McNair.
1924. Shallow, Thomas A., 1611 Spruce St.
1908. Shannon, Charles E. G., 1930 Chestnut St.
1928. Sharpe, John S., Haverford, Pa.
1928. Sharpless, Frederick C., Rosemont, Pa.
1897. Sharpless, William T., West Chester, Pa.
1931. *Sheehan, William C.
1932. Sheridan, Joyce T., 412 W. Durham St.
1943. Shewbrooks, Daniel M., Penn Mutual Life Ins. Co., 6th and Walnut Sts.
1936. Shipman, James Shelby, 255 S. 17th St.
1935. Shoemaker, Robert, 3rd., 68 Byberry Rd., Hatboro, Pa.
1939. *Shumway, Norman P.
1936. Shuster, Benjamin H., 1824 Pine St.
1941. Silcox, Louis E., 255 S. 17th St.
1903. Sinclair, John F., 4103 Walnut St.
1907. Sinkler, Francis W., 136 S. 16th St.
1928. Skillern, Samuel R., 1734 Pine St.
1933. Smelzer, Donald Campbell, Germantown Hosp., Penn and Chew Sts.
1929. *Smith, Austin T.
1933. Smith, Lauren Howe., 111 N. 49th St.
1936. Smith, Richard Manges, 4727 Oakland St.
1927. Smyth, Calvin Mason, Room 451, Methodist Hospital, Broad and Wolf Sts.
1938. Snodgrass, L. E., 318 Walnut St.
1941. Snyder, G. Gordon, Mermont Apts., Bryn Mawr, Pa.
1935. Sokoloff, Martin J., 255 S. 17th St., Phila.
1940. Soloff, Louis A., 2032 Pine St.
1935. Sommer, George N. J., 120 W. State St., Trenton, N. J.
1944. Sommer, George N. J., Jr., 120 W. State St., Trenton, N. J.
1928. Spaeth, Edmund B., 1930 Chestnut St.
1937. Spangler, John Luther, Devon, Pa.
1935. Spiegel, Ernest, 6807 Lawnton Ave., Oak Lane.
1929. Sponsler, Marshall B., 1737 Chestnut St.
1944. Stadie, William C., University Hospital.
1927. Starr, Isaac, 505 Cresheim Valley Rd.
1945. Stecher, H. Armin, 1510 Darby Rd., Upper Darby, Pa.
1936. Steinfield, Edward, N.E. Cor. 18th and Chestnut Sts.
1942. Stengel, Alfred, Jr., Newtown Square, Delaware County, Pa.
1914. Stewart, Thomas S., The Barclay, 18th and Rittenhouse Sq.
1941. Stewart, Winifred B., 2028 Delancey St.

* On active service.

1931. *Stiles, Merritt H.
1934. Stimson, Cheney M., 167 Harvey St., Germantown.
1925. Stokes, John H., 4228 Spruce St.
1928. Stokes, Joseph, Jr., 1740 Bainbridge St.
1943. Stokes, S. Emlen, 129 Chester Ave., Moorestown, N. J.
1923. Strecker, Edward A., 111 N. 49th St.
1923. Stroud, William Daniel, 1011 Clinton St.
1937. Strumia, Max M., Penn Valley, Narberth, Pa.
1933. Stuckert, Harry, 248 S. 21st St.
1937. Sturgis, Margaret C., 34 W. Montgomery Ave., Ardmore, Pa.
1927. Sturgis, Samuel Booth, 34 W. Montgomery Ave., Ardmore, Pa.
1934. Summey, Thomas J., 330 S. 9th St.
1930. Sunderman, F. William, 2210 Delancey St.
1936. Surver, James Miller, 1832 Spruce St.
1928. Swartley, William B., 6002 Greene St.
1934. Sweeney, John A., 1900 Rittenhouse Sq.
1944. Swenson, Paul C., Jefferson Hospital.
1943. Tassman, Isaac S., 136 S. 16th St.
1933. Taylor, Herbert W., Haverford, Pa.
1931. Taylor, Norman H., 100 W. Evergreen Ave.
1928. Thomas, J. Earl, Drexel Hill, Pa.
1907. Thomas, T. Turner, 1636 Francis St.
1942. Thompson, Wesley, D., Jr., 1416 S. Penn Square.
1927. Thorington, J. Monroe, 2031 Chestnut St.
1936. Thornton, Mary Bickings-, 2703 West Somerset St.
1936. Thorp, Francis Quicksall, 4900 Penn St.
1936. Thudium, William J., 136 S. 16 St.
1935. Tocantins, Leandro Maués, 45 Woodale Rd.
1945. Toland, Joseph J., Jr., 1241 W. Lehigh Ave.
1935. Toland, Owen J., Episcopal Hospital, Front and Lehigh Ave.
1941. Tompkins, Pendleton, 807 Spruce St.
1945. Tourish, William J., 1832 W. Venango St.
1936. Towson, Charles Emory, Germantown Professional Bldg.
1908. Tracy, Stephen E., 1930 Chestnut St.
1926. Tucker, Gabriel, 250 S. 18th St.
1938. Tuft, Louis, 1530 Locust St.
1933. Tumen, Henry J., 1900 Rittenhouse Sq.
1938. Turman, Christopher M., Wyncote, Pa.
1923. Turner, Creighton H., 1731 Pine St.
1945. Twyeffort, Louis H., 111 N. 49th St.
1929. Tyson, Ralph M., 255 S. 17th St.
1937. Uhle, Charles A. W., East Valley Green Rd., White Marsh, Pa.
1907. Ullom, Josephus T., Carpenter and Quincy Sts.
1937. *Vander Veer, Joseph B.
1937. Van Loon, Emily Lois, 1930 Chestnut St.
1933. Vastine, Jacob H. 2nd, 136 S. 16 St.
1912. Vaux, Norris Wistar, 807 Spruce St.
1940. Voegelin, Adrian W., Germantown Professional Bldg.
1941. *Vogel, Stoughton R.
1903. Wadsworth, William S., 3914 Baltimore Ave.

* On active service.

1927. Wagers, Arthur J., 1429 Spruce St.
1928. Wagoner, George W., Haverford Gables, Haverford, Pa.
1938. Waldman, Joseph, 216 E. Gorgas Lane.
1906. Walker, John K., Media, Pa.
1907. Walker, Warren, 136 S. 16th St.
1932. Walkling, Adolph A., 136 S. 16 St.
1904. Walsh, Joseph, 1811 Chestnut St.
1895. Watson, Arthur W., 2013 Locust St.
1932. Watt, Charles C., Jr., 6605 Wayne Ave.
1933. Waygood, James Jamison, 3464 School Lane.
1941. Weaver, Ruth H., 1719 Rittenhouse Square.
1930. Weeder, S. Dana, 6110 Greene St.
1920. Weidman, Fred D., 20 Tenby Rd., Llanerch, Pa.
1933. Weiss, Benjamin P., The Lenox, 13th and Spruce Sts.
1923. Weiss, Edward, 269 S. 19th St.
1935. Whelan, G. L., 2100 Walnut St.
1921. Whitaker, William, 6771 Germantown Ave.
1936. White, Ellen Pawling Corson-, 1820 Pine St.
1925. Widmann, Bernard P., 250 S. 18th St.
1936. Wilder, Theodore S., Germantown Professional Bldg., Greene and Coulter Sts.
1914. Willard, De Forest P., 1726 Spruce St.
1935. *Willard, John Harrington.
1939. Willauer, George, 6129 Greene St.
1907. Williams, Carl, School Lane and Greene St.
1924. Williams, Horace James, 5908 Greene St., Germantown.
1937. Williams, John C., 6370 Germantown Ave.
1920. Williams, Philip F., 2206 Locust St.
1927. Williamson, Ernest G., 6353 Woodbine Ave.
1921. Wilson, George, 133 S. 36th St.
1945. Wilson, John F., 1930 Chestnut St.
1942. Wilson, Lucius R., 1305 Morris Road, Wynnewood, Pa.
1937. Wilson, Ross B., 1820 S. Rittenhouse Sq.
1902. Wilson, Samuel M., 1930 Chestnut St.
1940. *Winchell, A. Vaughn.
1941. Wirts, C. Wilmer, 2017 Delancey St.
1904. Wister, James W., 5430 Germantown Ave.
1933. Wohl, Michael G., 1727 Pine St.
1944. Wolf, Lewis R., 3474 Frankford Ave.
1918. Wolferth, Charles C., S.E. Cor. 36th & Spruce Sts.
1942. *Wolman, Irving J.
1893. Wood, Alfred C., 2035 Walnut St.
1932. Wood, Francis C., 212 Laurel Lane, Haverford, Pa.
1900. Wood, George B., N.E. Corner 20th and Chestnut Sts.
1903. Wood, Horatio C., 319 S. 41st St.
1944. Wood, H. Curtis, Jr., Skippack Pk., Whitemarsh, Pa.
1897. Woodward, George, W. Willow Grove Ave., Chestnut Hill.
1928. Wright, Carroll S., 1402 Spruce St.
1937. Yaskin, Joseph C., 1832 Spruce St.
1943. Yawger, Nathaniel S., 1524 Chestnut St.
1941. Young, Barton R., Temple University Hosp.

* On active service.

1894. Zentmayer, William, 1930 Chestnut St.
1933. Zulick, J. Donald, Abington Memorial Hospital, Abington, Pa.

# Non-Resident Fellows

ELECTED

1903. Biggs, M. H., Rutherfordton, N. C.
1937. *Braceland, Francis J.
1908. Cadbury, William W., Lingnan University, Canton, China.
1936. Camero, Anthony R., 657 S. Westlake Ave., Los Angeles, Cal.
1936. Clarke, Francis Mann, 116 New St., New Brunswick, N. J.
1936. *Cooper, Melbourne J.
1897. Dorland, W. A. Newman, 1236 N. Dearborn Parkway, Chicago, Ill.
1905. Evans, Joseph S., Jr., 1300 University Ave., Madison, Wis.
1933. Fowler, Kenneth, 2535 Horton Ave., San Diego, Cal.
1935. Fretz, John Edgar, "Hillcrest" College Hill, Easton, Pa.
1913. Gates, Nathaniel, 10 Peterboro, Detroit, Mich.
1936. Guthrie, Donald, 118 S. Wilbur Ave., Sayre, Pa.
1902. Gwyn, Norman B., 109 Madison Ave., Toronto, Canada.
1936. Hatch, Lerleen Clement, 747 Ardmore Ave., Akron, O.
1928. Hayman, Joseph Marchant, Jr., Lakeside Hosp., 2065 Adelbert Rd., Cleveland, Ohio.
1892. Hinsdale, Guy, % The Postern, Brierwood La., Summerville, S. C.
1933. Hitzrot, Lewis H., Medical Director, Mercersburg Academy, Mercersburg, Pa.
1936. Hughes, Brady A., 5005 42d Place, North, Birmingham, Ala.
1899. Jopson, John H., Pawley's Island, S. C.
1931. Kinney, Willard H., 7300 Atlantic Ave., Ventnor, N. J.
1941. Lockwood, John S., Hamden, Conn.
1935. McGuire, Hunter H., 105 N. Braddock St., Winchester, Va.
1900. McReynolds, Robert Phillips, 213 S. Broadway, Los Angeles, Cal.
1936. Middleton, William Shainline, 2114 Adams St., Madison, Wisconsin.
1915. Musser, John H., 1430 Tulane Ave., New Orleans, La.
1937. Nicholson, Samuel T., 2d, The Hill School, Pottstown, Pa.
1905. Norris, George W., Dimock, Pa.
1926. Paul, John Rodman, Dept. Internal Medicine, Yale University, New Haven, Conn.
1907. Price, George E., Stimson Bldg., Seattle, Wash.
1904. Ravenel, M. P., 203 Westmount Ave., Columbia, Mo.
1936. *Reisinger, John A.
1907. Royer, B. Franklin, The Hall, R. D. 7, Chambersburg, Pa.
1913. de Schweinitz, George L., 85 E. Broad St., Bethlehem, Pa.
1941. Shands, Alfred R., Jr., Alfred I. duPont Institute, Rockland Rd., Wilmington, Del.
1932. Siegel, Alvin Erdreich, Medical Arts Building, Macon, Ga.
1934. *Stewart, Sloan G.
1900. Swan, John M., 457 Park Ave., Rochester, N. Y.
1930. Thorpe, Edward S., Jr., Medical Director, St. Paul's School, Concord, N. H.
1913. Vail, William Penn, Blairstown, N. J.
1897. Veasey, Clarence Archibald, 1569 Paulsen Medical and Dental Bldg., Spokane, Washington.
1931. Walker, Herschel Carey, 320 Park Ave., New York City, N. Y.
1903. Weber, Charles H., 3 Arch Bay, Laguna Beach, California.

* On active service.

# Honorary Fellows

Limited to Fifty, of Whom Twenty May be Foreigners

### American

ELECTED

1917. Miner, Charles Howard, B.S., M.D., Member of Board of Directors, Wilkes-Barre General Hospital; Board of Health, Wilkes-Barre; Board of Directors, White Haven Sanitarium Association and Penna. Tuberculosis Society. 264 S. Franklin St., Wilkes-Barre, Pa.

1936. Richards, Alfred Newton, PH.D., SC.D., M.D. (HON.), L.L.D., Professor of Pharmacology, School of Medicine, Vice-president in charge of Medical Affairs, Univ. of Pa. School of Medicine, Univ. of Pa., Phila.

1942. Russell, Frederick Fuller, M.D., Brig. Gen. Med. Corps, U. S. A. (Ret.). Harvard Medical School, Boston, Mass.

### Foreign

1937. Dale, Sir Henry Hallett, C.B.E., F.R.S., M.A., M.D., F.R.C.P., Director, National Institute for Medical Research, Hampstead, Eng. Mt. Vernon House, N.W. 3, Hampstead, London.

1924. Hopkins, Sir F. Gowland, M.D., Biochemical Department, University of Cambridge, Cambridge, England.

1922. McCarrison, Sir Robert, K.T., C.I.E., M.D., D.SC., LL.D., F.R.C.P., Major-General, Indian Medical Service (retired). 18 Linton Rd., Oxford, England.

### Honorary Associates

1942. Conklin, Professor Edwin G., Princeton University, Princeton, N. J.

1942. Donner, William Henry, Lincoln-Liberty Bldg., Philadelphia, Pa.

# Necrological List

| *Resident Fellows* | *Date of Election* | *Date of Death* |
|---|---|---|
| Robert S. Alston | January 9, 1933 | April 24, 1945 |
| Bernard I. Comroe | January 9, 1939 | September 14, 1945 |
| Edward Blanchard Hodge | February 2, 1905 | June 19, 1945 |
| William Hamilton Jefferys | November 5, 1913 | May 14, 1945 |
| *Roland N. Klemmer | May 7, 1934 | May 19, 1944 |
| Joseph McFarland | January 2, 1895 | September 22, 1945 |
| Henry Alexander Miller | October 4, 1944 | July 14, 1945 |
| Josef B. Nylin | May 8, 1933 | June 23, 1945 |
| Harold D. Palmer | May 8, 1933 | November 21, 1945 |
| George S. de Renyi | May 6, 1929 | August 24, 1945 |
| William John Ryan | January 7, 1929 | April 19, 1945 |
| J. Clinton Starbuck | December 1, 1909 | June 21, 1945 |
| Edward Q. Thornton | May 4, 1898 | January 17, 1945 |

| *Non-Resident Fellows* | *Date of Election* | *Date of Death* |
|---|---|---|
| W. P. Conaway | May 10, 1937 | January 23, 1945 |

* Died while on board ship somewhere in the South Pacific.

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